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13. ABSTRACT *(Maximum 200 words)*
In this prospective, randomized, double-blind study, investigators compared the incidence of postoperative nausea and vomiting (PONV) seen with neostigmine-glycopyrrolate versus edrophonium-atropine when used to reverse neuromuscular block. Forty-two American Society of Anesthesiologist (ASA) I or II women presenting for elective laparoscopy were randomly administered either neostigmine-glycopyrrolate (Group I) or edrophonium-atropine (Group II) at the end of surgery to reverse their neuromuscular block. The anesthetic regime was otherwise the same for both groups. Data collection began upon extubation and ended 12 hours later. Statistical analysis consisted of one-way ANOVA, Fisher's exact test, and Pearson's r. The significance level chosen was $p < 0.05$. Demographic characteristics were similar in both groups. Both groups experienced similar incidences of PONV and antiemetic rescue therapy use. Patients in Group I took an average of 46 minutes longer than patients in Group II to meet ASC discharge criteria ($p = 0.04$). A significant correlation was noted between Asian race ($n = 3$) and PONV in the PACU ($p < 0.001$) and in the ASC ($p < 0.001$). Hispanic race ($n = 3$) was positively associated with antiemetic rescue therapy use in the PACU. A history of motion sickness was positively correlated with PONV in the ASC ($p < 0.05$). Neostigmine (when combined with atropine) has been observed to be associated with a significantly higher incidence of PONV than edrophonium atropine. Neostigmine has a longer duration of action than atropine which may be responsible for a greater incidence of muscarinic side effects seen when these two drugs are used in combination. Neostigmine and glycopyrrolate share similar onsets and durations (as do edrophonium and atropine). This may account for the lack of a significant difference in the incidence of PONV seen between the two drug combinations in this study. Alternatively, a Type II error can not be ruled out due to the study's small sample size. It is not known why Group I took significantly longer than Group II to meet ASC discharge criteria. There was no correlation between this variable and the incidence of PONV.

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COMPARISON OF THE EFFECTS OF NEOSTIGMINE-GLYCOPYRROLATE VERSUS EDROPHONIUM-ATROPINE ON THE INCIDENCE OF POSTOPERATIVE NAUSEA AND VOMITING

By

Vincent Bogan, CPT, BSN, BA

Michael Luce, CPT, BSN

A Thesis

submitted in partial fulfillment

of the requirements for the degree of

Master of Science in Nursing

The University of Texas Health Science Center at Houston

School of Nursing

October, 1997

ABSTRACT:

In this prospective, randomized, double-blind study, investigators compared the incidence of postoperative nausea and vomiting (PONV) seen with neostigmine-glycopyrrolate versus edrophonium-atropine when used to reverse neuromuscular block. Forty-two American Society of Anesthesiologist (ASA) I or II women presenting for elective laparoscopy were randomly administered either neostigmine-glycopyrrolate (Group I) or edrophonium-atropine (Group II) at the end of surgery to reverse their neuromuscular block. The anesthetic regime was otherwise the same for both groups. Data collection began upon extubation and ended 12 hours later. Statistical analysis consisted of one-way ANOVA, Fisher's exact test, and Pearson's r. The significance level chosen was $p < 0.05$.

Demographic characteristics were similar in both groups. Both groups experienced similar incidences of PONV and antiemetic rescue therapy use. Patients in Group I took an average of 46 minutes longer than patients in Group II to meet ASC discharge criteria ($p = 0.04$). A significant correlation was noted between Asian race ($n = 3$) and PONV in the PACU ($p < 0.001$) and in the ASC ($p < 0.001$). Hispanic race ($n = 3$) was positively associated with antiemetic rescue therapy use in the PACU. A history of motion sickness was positively correlated with PONV in the ASC ($p < 0.05$).

Neostigmine (when combined with atropine) has been observed to be associated with a significantly higher incidence of PONV than edrophonium-

atropine. Neostigmine has a longer duration of action than atropine which may be responsible for a greater incidence of muscarinic side effects seen when these two drugs are used in combination. Neostigmine and glycopyrrolate share similar onsets and durations of action (as do edrophonium and atropine). This may account for the lack of a significant difference in the incidence of PONV seen between the two drug combinations in this study. Alternatively, a Type II error can not be ruled out due to the study's small sample size. It is not known why Group I took significantly longer than Group II to meet ASC discharge criteria. There was no correlation between this variable and the incidence of PONV.

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THE UNIVERSITY OF TEXAS
HOUSTON
HEALTH SCIENCE CENTER

The Committee for the
Protection of Human Subjects

NOTICE OF APPROVAL TO BEGIN RESEARCH November 15, 1996

HSC-SN-96-030- "Postoperative Nausea and Vomiting: Neostigmine-Glycopyrrolate vs. Edrophonium-Atropine as Neuromuscular Reversal Agent Combinations"
P.I.: Vincent Bogan, MSN Student; Cpt. Luce, 1LT Rosado, 1LT Svare

PROVISIONS: The research informed consent must be obtained separately from the surgical informed consent.

APPROVED: At a Convened Meeting

APPROVAL DATE: November 15, 1996 EXPIRATION DATE: October 31, 1997

CHAIRPERSON: Anne Dougherty, MD

Subject to any provisions noted above, you may now begin this research.

CHANGES - The P.I. must receive approval from the CPHS before initiating any changes, including those required by the sponsor, which would affect human subjects, e.g. changes in methods or procedures, numbers or kinds of human subjects, or revisions to the informed consent document or procedures. The addition of co-investigators must also receive approval from the CPHS. ALL PROTOCOL REVISIONS MUST BE SUBMITTED TO THE SPONSOR OF THE RESEARCH.

INFORMED CONSENT - Informed consent must be obtained by the P.I. or designee using the format and procedures approved by the CPHS. The P.I. must instruct the designee in the methods approved by the CPHS for the consent process. The individual obtaining informed consent must also sign the consent document.

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CHAPTER I

Introduction

Postoperative nausea and vomiting (PONV) are serious side effects of anesthesia and surgery. Postoperative nausea and vomiting are two of the most frequent causes of unanticipated hospital admissions, extended anesthesia recovery time and increased cost of care. On average, one third of all patients undergoing anesthesia experience significant postoperative nausea (Claybon, 1994). Women are especially at risk for PONV with a 2-3 fold increased incidence of PONV compared to males (Lerman, 1992). In particular, laparoscopic gynecological surgery is associated with a 40 - 70% incidence of PONV (Lerman).

PONV are associated with numerous complications such as wound dehiscence, electrolyte imbalances, and risk of pulmonary aspiration. Additionally, PONV is expensive for both hospitals and patients. A delayed hospital discharge due to PONV adds, on average, $415 to the cost of care (Carroll, Miederhoff, & Cox, 1994).

Numerous investigators have observed an increased incidence of PONV associated with the use of neuromuscular blocker reversal agents (Ding, Fredman, & White, 1994; Grasela et al., 1994; Kao, et al., 1992; King, Milazkiewicz, Carli, & Deacock, 1988; Watcha, Safavi, McCulloch, Tan, & White, 1995). Paralyzation with neuromuscular blocking drugs facilitates optimum intubation conditions and a motionless surgical field. Upon completion of surgery, the residual effects of a neuromuscular blocking drug are reversed with an anticholinesterase-antimuscarinic

drug combination. Reversal is necessary to restore normal neuromuscular function allowing the patient to move adequately and breathe unassisted. Nausea and vomiting associated with reversal of neuromuscular blockade are of particular interest to nurse anesthetists. In the period shortly after a reversal drug combination is given, airway reflexes may not have yet fully recovered. Nausea and vomiting occurring shortly after the reversal of neuromuscular block place the patient at a particularly high risk for pulmonary aspiration, a major cause of postoperative morbidity and mortality (Boeke, Delange, VanDruenen, & Langemeijer, 1994).

Investigators have observed a greater incidence of PONV associated with the use of reversal agent combinations, notably neostigmine-atropine (Ding et al., 1994; Kao, et al., 1992; King et al., 1988). Neostigmine has a slower onset of action and a longer duration of action than atropine. Accordingly, this reversal combination is rarely used in clinical practice. Neostigmine-glycopyrrolate and edrophonium-atropine are the two reversal-agent combinations in common use today. It is not known if the greater incidence of PONV observed with neostigmine-atropine would also be observed with the use of neostigmine-glycopyrrolate.

Only one study was found where investigators compared the incidence of PONV observed with neostigmine-glycopyrrolate versus edrophonium-atropine (Watcha et al., 1995). Investigation is needed to determine the incidence of PONV seen with these commonly used reversal combinations. These investigators compared the incidence of PONV observed with the use of neostigmine-glycopyrrolate versus

edrophonium-atropine for reversal of neuromuscular blockade in female outpatients undergoing elective laparoscopic surgery.

Statement of the Problem

Does the choice of the neuromuscular reversal agent combination affect the incidence of PONV? Will there be a difference in the incidence of PONV seen with neostigmine-glycopyrrolate versus edrophonium-atropine when used to reverse the effects of a neuromuscular blocking agent on adult female outpatients undergoing elective laparoscopic surgery (tubal ligation, cholecystectomy, or diagnostic gynecological laparoscopy)?

Physiological Framework

The Physiology of Nausea and Vomiting

A physiological model focusing on the vomiting center (VC), chemoreceptor trigger zone (CTZ), barrier pressure (BP) and lower esophageal sphincter tone (LES) provides a useful framework to examine and discuss the causes of PONV. As early as 1953, Borison and Wang demonstrated the existence of a vomiting center and a chemoreceptor trigger zone in the brain stem. As seen in Figure 1, the vomiting center may be stimulated directly through afferent input or indirectly stimulated via the chemorecepter trigger zone. Afferent input to the VC may arise from various locations including the gastrointestinal tract and the CTZ. The CTZ is stimulated by blood-borne emetics.

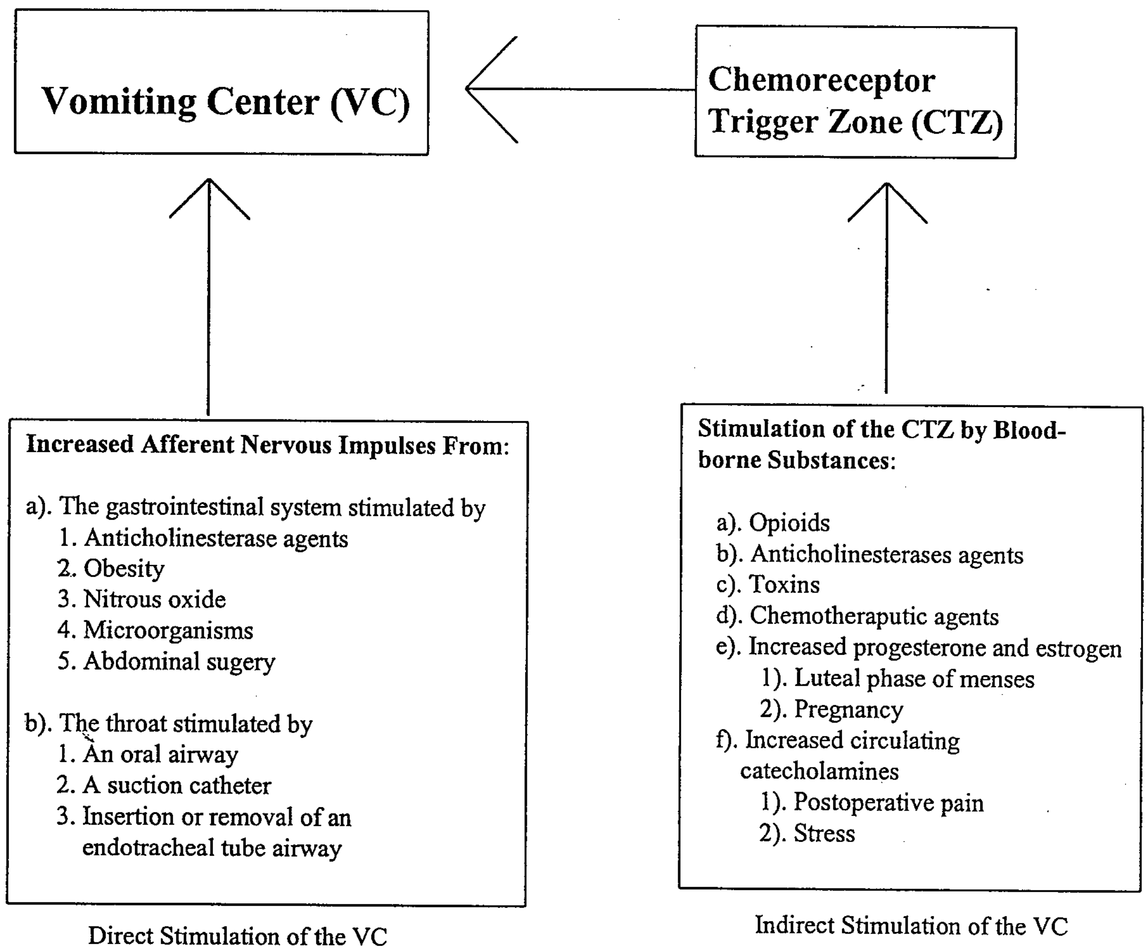

Figure 1. Stimulation of vomiting center (modified from Brunton, 1996).

The causes of PONV are multifactorial (Figure 1). The vomiting center may be stimulated directly via afferent impules associated with conditions such as obesity (Andrews, 1992; Lerman, 1992; Mecca, 1991) and abdominal surgery (Andrews; Honkavaara, Lehtinen, Hovorka, & Kortilla, 1991; Lerman; Pataky, Kitz, Andrews, & Lecky, 1988; Ramsey, McDonald, & Faragher, 1994). The CTZ may be stimulated by high circulating levels of catecholamines as seen with postoperative pain (Anderson & Krohg , 1976; Andrews; Woolf, 1991), menstrual cycle hormone fluctuations (Andrews; Carpenter, Briggs, Knox, & Strominger, 1988; Honkavarra et al.; Lerman; Palazzo & Strunin, 1984; Ramsey et al.), and opioid use (Andrews; Barnes, Bunce, Naylor, & Rudd, 1991; Lerman; Nimmo, 1984). Neuromuscular blocker reversal agent use is believed to increase the risk of PONV through both stimulation of the vomiting center as well as the CTZ (Ding et al., 1994; Grasela et al., 1994; Kao et al., 1992; King et al., 1988; Watcha et al., 1995). Other factors known to increase the incidence of PONV include co-existing disease (Andrews; Lerman; Rosecrans et al., 1996; Stoelting & Miller, 1994), anxiety (Andrews; Lerman), surgical duration (Andrews, Lerman), use of nitrous oxide (Andrews; Lerman; Stoelting & Miller, 1994), activity (Anderson & Krohg; Andrews; Stoelting & Miller), and intravascular fluid volume and blood pressure (Andrews).

In order for PONV to occur, the pressure within the stomach (intragastric pressure), must exceed the pressure maintained by the lower esophageal sphincter. Barrier pressure is the difference between the lower esophageal sphincter pressure and the intragastric pressure. A rise in intragastric pressure, or a lowering of the lower

esophageal sphincter pressure, lowers the barrier pressure and increases the risk of gastric contents entering the esophagus. Stimulation of the vomiting center causes forceful abdominal contractions resulting in a rapid rise in gastric pressure. When the intragastric pressure exceeds the lower esophageal sphincter pressure, the result is the forceful expulsions of contents from the stomach. Figure 2 provides a graphic representation of the mechanisms by which neuromuscular blocker reversal agents are believed to cause nausea and vomiting.

Reversal Agent Effects on the Vomiting Center

Anticholinesterase drugs such as neostigmine or edrophonium, given by themselves, cause gastric spasm which lowers the barrier pressure and may increase afferent input to the vomiting center resulting in PONV. Additionally, the CTZ is stimulated directly by these drugs via the blood stream. Antimuscarinic agents, such as atropine and glycopyrrolate, decrease the lower esophageal sphincter tone, thereby lowering the barrier pressure, also predisposing the patient to the risk of reflux and pulmonary aspiration (Brocke-Utne, Downing, Welman, Dimopoulos, & Moshal, 1978; Cotton & Smith., 1981; Dent et al., 1980; Fisher, Malmud, Roberts, & Lobis, 1977; Turner, & Smith, 1985).

Unlike glycopyrrolate, atropine is lipid soluble and able to cross the blood-brain barrier. Atropine may thus antagonize vagal afferent impulse transmission to the vomiting center and thereby have an antiemetic effect (Mirakhur & Dundee, 1981; Palazzo & Strunin, 1984; Stoelting, 1991). When an anticholinesterase drug is given together with an antimuscarinic drug, the combined effect of both drugs on the

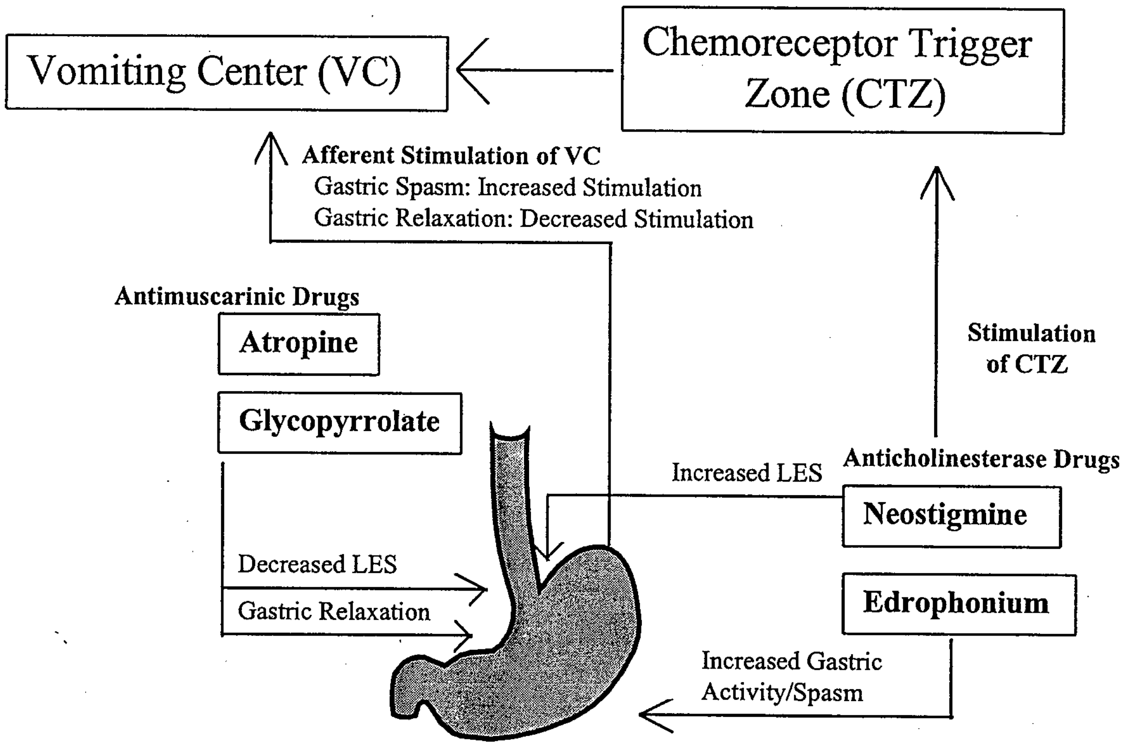

Figure 2. Physiological Effects of Reversal Agents on PONV (Modified from Brunton, 1996). Anticholinesterase agents (given without an accompanying antimuscarinic agent) cause gastric spasms which result in afferent impulse transmission to the vomiting center as well as a decrease in the barrier pressure (lower esophageal sphincter tone [LES] - gastric pressure). Anticholinesterase drugs may also increase the risk of PONV through stimulation of the CTZ. Antimuscarinic agents lower the LES (and consequently the barrier pressure) which may increase the risk of PONV.

gastrointestinal system is minimal, assuming that both drugs share similar onsets of action and durations of effect.

Reversal of Neuromuscular Blockade

Acetylcholine is a neurotransmitter released at the neuromuscular junction by motor neurons. At the neuromuscular junction, acetylcholine stimulates nicotinic receptors causing skeletal muscle stimulation and allowing voluntary movement to occur. A nondepolarizing neuromuscular blocking drug causes muscle relaxation by blocking the acetylcholine receptors at the neuromuscular junction (Stoelting, 1991).

At the end of surgery, anticholinesterase drugs are used to reverse neuromuscular block by allowing acetylcholine to accumulate at the neuromuscular junction and oppose any remaining effects of a neuromuscular blocker drug. Anticholinesterases accomplish this by inhibiting the enzyme acetylcholinesterase which normally inactivates acetylcholine. The resulting accumulation of acetylcholine stimulates the skeletal muscle nicotinic receptors and helps to overcome any residual blockade. Unfortunately, anticholinesterase drugs also allow acetylcholine to accumulate at organ sites such as the heart, lungs, and gastrointestinal tract. At these locations, excess acetylcholine stimulates organ muscarinic receptors and can cause serious side effects such as bradycardia, bronchospasm, and increased gastric smooth-muscle tone and spasm, and PONV.

To prevent these effects, an antimuscarinic drug is given in combination with the anticholinesterase agent. Antimuscarinics prevent the deleterious effects of anticholinesterase agents by blocking the muscarinic receptors preventing the excess

muscarinic stimulation that would otherwise be seen when an anticholinesterase is given alone. Antimuscarinics do not block acetylcholine receptors at the neuromuscular junction and, therefore, do not interfere with the desired action of the co-administered anticholinesterase agent (Savarese, Miller, Lien, & Caldwell, 1994; Stoelting, 1991).

As seen in Figure 2, both anticholinesterase and antimuscarinic drugs may increase the risk of PONV. Given together, however, their effects at vital organ receptor sites cancel each other out and allow near-normal organ function (e.g. normal LES and BP). As shown in Figure 3, this may be the case only for drug combinations in which the individual anticholinesterase and antimuscarinic agents share similar onsets and durations of action. Dissimilar onsets and durations of action allow the undesirable effects seen when one drug exerts its effect in the absence of the effects of its antagonist (see the drawing on the left in Figure 3).

Atropine has a faster onset of action than neostigmine, but a shorter duration of action. Accordingly, when these two drugs are given together, one initially may see excess antimuscarinic effects due to atropine (Gyermek, 1978). These effects are followed by a period of nearly normal physiologic function where both drugs act in opposition to each other, preventing either excess antimuscarinic or muscarinic side effects. Because neostigmine's duration of action is longer than atropine, the terminal drug effect may be an excess of muscarinic stimulation. The individual agents in the combinations neostigmine-glycopyrrolate and edrophonium-atropine share similar onsets and durations (see the drawing on the right in Figure 3). Accordingly, fewer

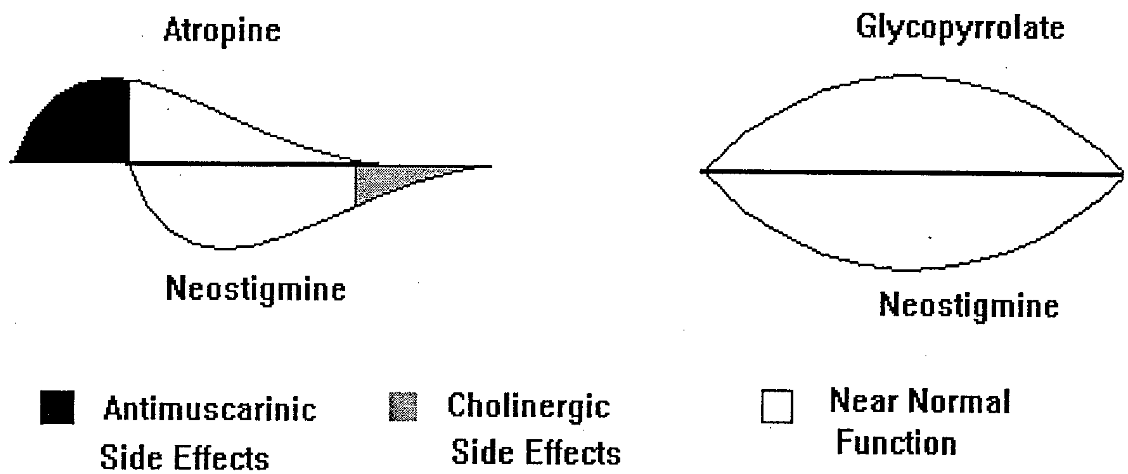

Figure 3. Relationship between drug onsets and duration and associated side effects. Edrophonium-atropine has a similar onset and duration profile as that depicted above for neostigmine-glycopyrrolate (adapted from Gyermek, 1978).

muscarinic or antimuscarinic side effects are associated with their use (Bevan, Bevan, & Donati, 1988; Gyermek, 1978).

Purpose

The purpose of this study was to compare the incidence of PONV seen following elective, outpatient, female laparoscopic surgery when using neostigmine-glycopyrrolate versus edrophonium-atropine for reversal of neuromuscular block.

Definition of Terms

Anesthesia time. Anesthesia time refers to the time during which the patient is under the care of an anesthesia care provider. Operationally, anesthesia time is defined as the time that the anesthesia provider starts to provide care for the patient in the OR holding area until the care of the patient is turned over to the PACU nursing staff.

Nausea. Nausea refers to an unpleasant subjective sensation associated with the urge to vomit. Operationally, nausea is the patient's subjective complaint of nausea recorded on the In-hospital Data Form or on the Rhodes Index of Nausea and Vomiting II.

Postoperative period. The postoperative period begins upon completion of surgery and anesthesia. Operationally, the postoperative period is defined as the first twelve hours after extubation of the patient.

Retching. Retching is similar to vomiting, but without the expulsion of gastric contents. Retching involves labored, rhythmic contractions of the respiratory muscles, including the diaphragm, chest walls, and abdominal wall muscles. Operationally, retching is defined as apparent attempts to vomit which are not accompanied by the

expulsion of gastric contents occurring upon extubation until 12 hours later. All instances of retching will be recorded as a vomit incidence on the In-hospital Data form or the Rhodes Index of Nausea and Vomiting.

Surgical time. Surgical time refers to the period of time during which surgery is performed. Surgical time is operationally defined as the time from the first surgical incision until dressing application.

Time to meet discharge criteria. Time to meet discharge criteria refers to the time it takes the patient to meet PACU and ASC criteria for discharge. The time to meet PACU discharge criteria is operationally defined as the time it takes the patient to demonstrate the ability to maintain room air arterial oxygen saturation of 93% or greater, verbalize that their pain level is tolerable, maintain a body temperature > 95 degrees, become alert and oriented to time, place, and situation, and maintain stable vital signs (heart rate and blood pressure) within 30% of preoperative values. The time to meet ASC discharge criteria is operationally defined as the time it takes the patient to tolerate (without emesis) 120 cc of clear fluids by mouth (apple juice or water), void, and not complain of nausea or uncontrolled pain. In both the PACU and the ASC, all patients are required to stay a minimum of 30 minutes regardless of their ability to otherwise meet discharge criteria.

Vomiting. Vomiting refers to forceful expulsion of gastric contents from the mouth produced by powerful sustained contraction of the abdominal muscles, descent of the diaphragm, and opening of the lower esophageal sphincter. Operationally, vomiting is the observation of gastric contents exiting the mouth or nose from the time

of extubation until twelve hours later. The word emesis may be substituted for vomiting without any change in meaning or operational definition.

Null Hypothesis

There is no difference in the incidence of PONV following elective laparoscopic surgery (tubal ligation, cholecystectomy, or diagnostic gynecological laparoscopy) in women using either neostigmine-glycopyrrolate or edrophonium-atropine for reversal of neuromuscular block.

Significance of the Problem.

PONV is one of the most common complications seen with outpatient surgeries (Hirsch, 1994). Serious complications of vomiting include pulmonary aspiration of stomach contents, fluid and electrolyte imbalances, and wound dehiscence. An emetic event may also precipitate alterations in heart rate and blood pressure, and an increase in the patient's level of pain (Reigle, Leveque, Hagan, Gerbasi & Bhatka, 1995).

Even in the absence of complications, patients find nausea and vomiting distressful and extremely unpleasant. Many patients perceive PONV to be more debilitating than the effects of their surgical procedure (Hirsch, 1994). The results of a satisfaction survey conducted by a civilian hospital in Honolulu, Hawaii found PONV to be their patients' most common complaint. These patients appeared to expect and accept the presence of postoperative pain, but did not expect to experience PONV (Mathias, personal communication, May 10, 1997).

In addition to the physical and psychological complications of PONV are the financial costs of PONV which affect both hospitals and their patients. PONV have been shown to prolong recovery room stay, disrupt patient flow, and increase per-patient institutional costs. Costs of PONV to the hospital were quantified by Carroll et al. (1994) as $15 per patient for additional personnel, drugs, and supplies; $7 per patient for additional nursing care needed in the postanesthesia care unit (PACU); and $415 per patient for lost revenue when patients have an extended stay in the PACU in surgical centers operating at capacity. Costs to patients include costs of additional treatment and lost wages due to missed work (Hirsch, 1994).

Reversal of neuromuscular blockade with anticholinesterases such as neostigmine and edrophonium facilitates quick recovery, but may have serious side effects such as PONV. Although research suggests an increased incidence of PONV associated with the use of neostigmine versus edrophonium (Grasela et al., 1994; Kao et al., 1992; Watcha et al., 1995), only one study was found concerning the recommended reversal combinations neostigmine-glycopyrrolate versus edrophonium-atropine and their incidence of PONV (Watcha et al., 1995).

Therefore, the two commonly used drug combinations of edrophonium-atropine and neostigmine-glycopyrrolate were compared to discern if either combination is associated with a greater incidence of PONV. Further research into this area will assist the anesthesia care provider to choose the reversal modality associated with the least incidence of PONV.

Assumptions

1. Nausea and vomiting are the result of physical, pharmacological, and/or emotional factors.

2. Nausea and vomiting correlate in a negative manner with patient satisfaction.

3. Nausea and vomiting are phenomena that anesthesia care providers desire to minimize.

4. Patients who experience nausea in the Postanesthesia Care Unit (PACU) or Ambulatory Surgical Center (ASC) will report this symptom to their care provider.

5. PACU and ASC nurses will accurately complete the study data forms.

6. Patients will accurately record incidents of PONV on the RINV-2 self-report forms.

Limitations

1. Data collection was performed by several investigators as well as by the nursing staffs in the PACU and the ASC. Although the technique was standardized, variability among the investigators and nursing staff cannot be ruled out. To minimize this, the PACU and ASC staff were instructed in the use of the data collection form. Throughout the study, quality control checks were performed to check the data forms. At the end of the study, all patients' PACU and ASC records were checked to verify the information on the data collection forms.

2. The population studied consisted of women undergoing elective laparoscopic tubal ligations, laparoscopic cholecystectomies, or diagnostic

gynecological laparoscopies. The use of this specific population and surgical procedure could limit the generalizability of the results to other populations.

3. The study did not have a protocol for the postoperative treatment of PONV and pain in the PACU and ASC. This increased the chances of extraneous variables such as opioid analgesia or the use of various antiemetics of differing efficacy influencing the results of the study. Data analysis, however, found both groups to be similar regarding the use of postoperative pain and antiemetic therapy.

4. The 42 subjects in the study were significantly less than the 120 needed per power analysis prediction. Accordingly, the lack of significant findings between the use of the two study drugs and the incidence of PONV may be due to a Type II error.

5. In several cases, the standardized anesthesia protocol was implemented by an anesthetist who was not otherwise involved in this study. This increased the possibility of protocol violations and differences in the implementation of the protocol. To minimize the possibility of protocol violations, all anesthetists were briefed regarding the protocol prior to each case. Each provider was also given a written copy of the protocol. Quality control checks were performed on a weekly basis to check the data forms for protocol violations. Additionally, at the end of the study, each patient's anesthesia record was examined for evidence of protocol violation. Twelve patients were removed from the study due to inadvertent protocol violations.

Summary

Nausea and vomiting are central concerns to patients, health-care providers and health-care organizations. PONV occurring after reversal from neuromuscular

blockade, before airway reflexes have fully recovered, is of particular significance. This is when the patient may be most predisposed to pulmonary aspiration (Boeke et al., 1994).

Kao et al. (1992) noticed a significant difference in the incidence of PONV between the use of neostigmine-atropine versus edrophonium-atropine. Ding et. al. (1994) and King et al. (1988) observed neostigmine-atropine to be associated with greater PONV when compared to spontaneous reversal of neuromuscular block. Only one study, however, was found comparing the more commonly used reversal agent combination neostigmine-glycopyrrolate with edrophonium-atropine (Watcha et al., 1995). A study comparing the two commonly used reversal combinations, neostigmine-glycopyrrolate and edrophonium-atropine, may provide additional information so anesthesia care providers can better select the reversal modality associated with the lowest incidence of PONV.

CHAPTER II

Review of Literature

The use of neuromuscular blocker reversal agents has been shown to significantly increase the incidence of PONV (Ding et al., 1994; Grasela et al., 1994; Kao et al., 1992; King et al., 1988; Watcha et al., 1995). The results from some studies suggest that PONV may be reduced by using edrophonium rather than neostigmine as the anticholinesterase component of the reversal agent combination (Grasela et al.; Kao et al.).

PONV is a complex problem with many variables which may influence its incidence. Causes of PONV related to the patient, the surgery, the anesthetic, and postoperative factors are discussed. Current theory and standard of practice are reviewed regarding the selection of appropriate drugs to use in combination with each other to safely reverse neuromuscular blockade. Comparison studies which evaluate the effects of reversal agents on the incidence of PONV are then discussed.

While there have been studies which have evaluated the effects of different reversal agents on PONV, these may be of little clinical significance because they evaluated the use of neostigmine-atropine (Boeke et al., 1994; Huang et al., 1993; Kao et al., 1992; King et al., 1988) which is a drug combination not commonly used in clinical practice. Only one study was found comparing the two clinically used and recommended reversal agent combinations of edrophonium-atropine versus neostigmine-glycopyrrolate (Watcha et al., 1995).

Etiology of Nausea and Vomiting

Many factors influence the occurrence of PONV. Variables affecting PONV may be specific to the patient, the surgery, the anesthesia, or the postoperative period (Watcha & White, 1992).

Patient Related Factors

Many variables having nothing to do with the particular anesthetic administered may affect the occurrence of PONV. These include age, gender, obesity, co-existing disease, and anxiety.

1. Age: The general incidence of PONV is highest in children. (Lerman, 1992). This may reflect their greater degree of parasympathetic tone. The incidence of PONV decreases with age. The risk for PONV remains steady throughout adulthood (Lerman) but may decrease after age 50 (Cohen, Duncan, DeBoer, & Tweed, 1994).

2. Gender: Women are noted to have a 2-3 fold increased incidence of PONV as compared to men (Andrews, 1992; Lerman, 1992). According to Andrews, women are up to 4 times more likely to experience PONV during the occurrence of menses. The literature does not clearly indicate, however, which phase of the menstrual cycle most predisposes a patient to experience PONV. The greatest incidence of PONV may be seen during the luteal (postovulatory) phase of menses (Lerman) or during the occurrence of menses (Andrews). The increased incidence of PONV seen in premenopausal women is believed to be due to progesterone and estrogen hormone level fluctuations which increase women's sensitivity to virtually all emetogenic

substances (Andrews). Several investigators found no statistically significant difference between the phase of the menstrual cycle and the incidence of PONV (Gratz et al., 1996; Rosecrans et al., 1996). Postmenopausal women are not noted to be at a greater risk for PONV than males (Beattie, Buckley, & Forrest, 1991).

3. Obesity: Obese patients appear to be at increased risk for PONV (Andrews, 1992, Lerman, 1992, Mecca, 1991). Obese patients often have incompetent lower esophageal sphincters (LES) with resultant lower barrier pressure and a predisposition to regurgitate. Additionally, large body fat stores provide a reservoir for anesthetic medications to accumulate (i.e. opioid medications) which allows drugs to exert a prolonged effect postoperatively (Stoelting & Miller, 1994). According to Lerman, obesity in itself may not predispose the patient for PONV. Difficulty anesthetizing obese patients may be the reason that a greater incidence of PONV is seen. Obesity is often associated with difficult mask ventilation which predisposes the patient to gastric distention and emesis (Lerman; Stoelting & Miller).

4. Co-existing disease or medical conditions: Patients with a history of motion sickness have a increased risk of experiencing PONV (Andrews, 1992; Lerman, 1992; Rosecrans et al., 1996). Pregnancy is also associated with increased PONV (Lerman). Conditions interfering with gastrointestinal motility such as gastroparesis seen in advanced diabetic patients are also associated with increased risk of PONV (Stoelting & Miller, 1994). Patients with incompetent lower esophageal sphincters such as those with hiatal hernia are likewise at greater risk (Lerman).

5. Anxiety: Anxiety, common before surgery, is associated with an increased incidence of PONV (Andrews, 1992; Lerman, 1992). Anxiety is accompanied by catecholamine release from the adrenal medulla. Catecholamines are believed to stimulate the CTZ resulting in nausea and vomiting (Lerman). Sedation has been noted to surpress nausea and vomiting (Andrews).

Surgical Related Factors

1. Surgical site: Intraabdominal surgery including laparoscopy is associated with increased risk for PONV (Honkavaara et al., 1991; Lerman, 1992; Pataky et al., 1988; Ramsey et al., 1994). Cholecystectomy surgery and larparoscopic gynecological surgery are associated with up to a 70% and 77% incidence of PONV respectively (Lerman). Proposed reasons for such high occurrences of PONV include traction on and manipulation of the abdominal viscera resulting in an increase in vagal afferent stimuli to the vomiting center (Andrews, 1992). A greater incidence of PONV has also been observed with surgery involving the head, eyes, ears, and throat (Lerman; Stoelting & Miller, 1994).

2. Surgical duration: Surgical duration is positively correlated with an increased incidence of PONV (Rosecrans et al., 1996). This may be due to the patient's longer exposure to anesthetic agents, prolonged fasting, and the increased pain associated with longer surgery (Lerman, 1992).

3. Gastric decompression: Evacuating the stomach with an oral gastric tube is not believed to decrease the incidence of PONV unless gastric distention was initially present. Gastric suction may attenuate the incidence of PONV seen in patients who

experience gastric distention due to difficult mask ventilation (Lerman, 1992). Conversely, Lerman also noted that a gastric tube may predispose a patient to PONV by irritating the gastric mucosa or by stimulating the duodenum.

Anesthesia Related Factors

1. General anesthesia. General anesthesia is associated with a greater incidence of PONV than is regional or local anesthesia (Andrews, 1992; Stoelting & Miller, 1994). The state of general anesthesia itself, irrespective of what agents are used, may contribute to the occurrence of PONV. General anesthesia renders a patient into a greater state of immobility than that seen in normal sleep. This degree of immobility results in decreased tonic afferent discharge from the vestibular apparatus in the inner ear. Sudden movement after anesthesia may cause a sudden vestibular discharge of afferent impulses to the brain that stimulates the vomiting center and causes PONV (Andrews).

2. Anesthetic medications: Intraoperative opioid use has been positively associated with PONV. Opioids occupy mu receptor sites in the CTZ resulting in stimulation of the vomiting center (Andrews, 1992; Barnes et al., 1991; Lerman, 1992; Nimmo, 1984; Stoelting, 1991). Such occupation of mu receptors may also serve to sensitize the CTZ to other emetogenic stimuli (Andrews). Opioids also increase the incidence of PONV by decreasing gastric motility with subsequent increased gastric pressure and distention and by sensitizing the vestibular apparatus in the inner ear. Conversely, in some instances, opioids have been found to be antiemetogenic, because the presence of pain postoperatively is also associated with PONV. Patients

experiencing pain have greater circulating levels of catecholamines which stimulate the CTZ and result in PONV. In such instances, administration of an opioid analgesic has been observed to relieve nausea (Andersen & Krohg, 1976). The use of naloxone to reverse the effects of opioids supports the antinausea effects of opioids. Naloxone is a mu receptor antagonist drug having no emetogenic properties of its own. Sudden reversal of the effects of an opioid with naloxone, however, is often accompanied by nausea and vomiting (Andersen & Krohg).

The use of nitrous oxide is believed to increase the incidence of PONV. Possible mechanisms for this include effects of nitrous oxide such as gastric distention, middle ear pressure changes, and catecholamine release (Andrews, 1992; Lerman, 1992; Stoelting, 1991; Stoelting & Miller, 1994). Other inhalational agents may also contribute to the incidence of PONV. Animal study findings suggest that halothane may increase the risk of PONV by altering brain serotonin levels and by decreasing the tone of the lower esophageal sphincter, thus, lowering the barrier pressure (Andrews).

Anticholinesterases are believed to contribute to the incidence of PONV through muscarinic stimulation of the gastrointestinal tract. PONV result from marked stimulation of the vomiting center by vagal afferents as well as via stimulation of the CTZ via the drug in the blood stream (Andrews, 1992).

<u>Postoperative Related Factors</u>

1. Pain: As discussed above, the release of catecholamines associated with

painful stimuli stimulates the CTZ and may result in PONV (Anderson & Krohg , 1976; Andrews, 1992; Woolf, 1991).

2. Opioid analgesics: As with intraoperative opioid analgesics, opioids administered in the postoperative period stimulate mu receptors in the CTZ which may result in PONV. Opioid pain medications administered throughout a patient's postoperative stay in the hospital and those taken at home after discharge may contribute to the incidence of PONV seen (Andrews, 1992; Barnes et al., 1991; Lerman, 1992; Nimmo, 1984; Stoelting, 1991).

3. Activity: General anesthesia and opioids may predispose the patient for vestibular disturbances resulting in PONV. The CTZ also receives afferent input from cranial nerve VII (the vestibulocochlear nerve). Opioids may occupy mu receptors on cranial nerve VII and sensitize it. Subsequent movement may then result in increased afferent impulses sent to the vomiting center. This mechanism is most relevant during the later stages of recovery from anesthesia when the patient is more mobile (Andersen & Krohg, 1976; Andrews, 1992). Opioids may be less emetogenic in patients who are on complete bed rest (Stoelting & Miller, 1994).

4. Intravascular fluid volume and blood pressure: Preoperative fasting, surgical and anesthetic related fluid losses, and various medications given intraoperatively increase the risk of postoperative hypotension. Decreased intravascular volume and hypotension have been observed to result in nausea and vomiting. Possible mechanisms include an associated increase in blood catecholamine levels which stimulate the CTZ and an increase in cardiac vagal output which stimulates the

vomiting center (Andrews, 1992). A common clinical example of this is the nausea and vomiting that is often seen with drops in blood pressure accompanying spinal anesthesia. The PONV seen are promptly relieved by establishing a normal blood pressure with the use of ephedrine (Andrews).

The Use Of Combination Drugs to Reverse Neuromuscular Block

Edrophonium-atropine and neostigmine-glycopyrrolate are the two major reversal agent combinations recommended for use in the reversal of neuromuscular blockade (Savarese et al., 1994). The anticholinesterase actions of edrophonium and neostigmine reverse neuromuscular blockade by increasing the amount of acetylcholine in the neuromuscular junction. Both drugs inhibit acetylcholinesterase, the enzyme that inactivates acetylcholine. More acetylcholine is then available to compete with the neuromuscular blocker for the occupation of muscle nicotinic receptor sites, allowing restoration of normal muscular function following surgery. Unfortunately, the effects of high accumulations of acetylcholine at organ sites such as bronchial and gastrointestinal smooth muscle and cardiac muscle result in undesirable side effects. Deaths attributable to these side effects have occurred when neostigmine or glycopyrrolate were administered alone (Bevan et al., 1988; Bevan & Donati, 1992; Savarese et al.). Accordingly, administration of an antimuscarinic drug in combination with an anticholinesterase drug allows for safer reversal of neuromuscular blockade.

Antimuscarinic drugs such as atropine or glycopyrrolate block the muscarinic receptor sites at organs including the heart, bronchi, and gastrointestinal tract without interfering with the nicotinic receptors at the neuromuscular junction. Given by

themselves, antimuscarinic drug side effects include tachycardia, drying of oral secretions, and inhibition of gastric motility and tone. Given in combination with an anticholinesterase (e.g. neostigmine or edrophonium) these effects are opposed by the effects of the anticholinesterase drug. Ideally, both drugs' opposing side effects cancel each other out and do not interfere with vital-organ function during the reversal of neuromuscular blockade (Bevan et al., 1988; Bevan & Donati, 1992; Savarese et al., 1994). The reversal agent combinations edrophonium-atropine and neostigmine-glycopyrrolate are associated with fewer side effects than other combinations such as edrophonium-glycopyrrolate or neostigmine-atropine (Gyermek, 1978).

Reversal of Neuromuscular Block: Current Practice

The reversal drug combinations neostigmine-glycopyrrolate and edrophonium-atropine are both the reversal drugs of choice in clinical practice (Bevan & Donati, 1992; Savarese et al., 1994). Despite this, many studies have used neostigmine in combination with atropine in an effort to determine the effects of reversal therapy on the incidence of PONV (Boeke, et al., 1994; Huang et al., 1993; Kao et al., 1992; King et al., 1988). Some study findings suggest a significant reduction of PONV may be achieved by the use of a reversal combination using the anticholinesterase edrophonium versus neostigmine (Grasela et al., 1994; Kao et al., 1992; Watcha et al., 1995). Only one study was found that specifically compared the effects of edrophonium-atropine versus neostigmine-glycopyrrolate on PONV (Watcha et al.). Therefore, more studies are needed to compare the effects of edrophonium-atropine

versus neostigmine-glycopyrrolate on PONV, because these are the reversal combinations commonly used in clinical practice.

Incidence of PONV Associated With Neuromuscular Blocker Reversal agents

Various investigators have compared the incidence of PONV associated with the use of an anticholinesterase-antimuscarinic drug combination versus spontaneous recovery (allowing the block to subside with time; Boeke et al., 1994; Ding et al., 1994;

Grasela et al., 1994; Kao et al., 1992; King et al., 1988; Watcha et al., 1995). Investigators have also observed the incidence of PONV associated with the use of one particular reversal drug combination versus another (e.g. edrophonium-atropine versus neostigmine-atropine; Huang et al., 1993; Kao et al.).

Several investigators have observed an increased incidence of PONV ($p < .05$) associated with the use of neostigmine-glycopyrrolate (Ding et al., 1994; Watcha et al., 1995) or neostigmine-atropine (Kao et al., 1992; King et al., 1988) compared to the incidence of PONV seen with spontaneous reversal from neuromuscular blockade. Boeke et al. (1994) observed no significant difference in the incidence of PONV with the use of neostigmine-atropine compared with spontaneous reversal. Other investigators have observed reversal agent combinations using the anticholinesterase agent edrophonium to have lower (Grasela et al., 1994) or equal (Kao et al.; Watcha et al.) incidences of PONV as compared to spontaneous reversal ($p < .05$). Limitations included the use of small sample sizes, heterogeneous surgical procedures, and failure to monitor extraneous variables such as the phase of the menstrual cycle in female

populations. Furthermore, several of the investigators drew their conclusions based on the use of neostigmine-atropine (Ding et al., 1994; Kao et al., 1992; King et al., 1988), a reversal combination which is neither recommended nor commonly used in clinical practice (Bevan & Donati, 1992; Savarese et al., 1994).

Neostigmine versus Spontaneous Reversal

Ding et al. (1994), Kao et al. (1992), King et al. (1988), and Watcha et al. (1995) found a significantly increased incidence of PONV associated with the use of neostigmine ($p < .05$). Ding et al. and Watcha et al. studied neostigmine-glycopyrrolate while Kao et al. and King et al. studied neostigmine-atropine. Study weaknesses included small group sizes ($n \leq 20$; Ding et al.; Kao et al.; King et al.) and the use of neostigmine-atropine as a study drug (Kao et al.; King et al.). Because neostigmine-atropine is a reversal combination not recommended for clinical use the study results have questionable clinical relevance.

Ding et al. (1994) observed a 42% versus 25% incidence of emesis in the PACU between the use of neostigmine-glycopyrrolate and spontaneous reversal ($p < 0.05$). In an attempt to control for extraneous variables, Ding et al. removed all patients who developed PONV after administration of morphine for pain relief. This resulted in their sample sizes becoming less than 15 per group. It can not be assumed that predisposing factors for PONV work in isolation of each other. The presence of one PONV risk factor may increase the effect that a second risk factor exerts (Lerman, 1992). Could the use of one reversal agent versus another cause a patient to be more predisposed to experience PONV after opioid administration? If this is possible, then it

may have been inappropriate to remove such patients from the study. The results reported by Ding et al.'s study are further weakened by the fact that the study drug administration was not blinded. Ding et al.'s study is, thus, weakened due to small group sizes, weaknesses in methodology, and the unblinded nature of the study drug administration.

Kao et al. (1992) studied the incidence of PONV in premenopausal women. They observed an 37% versus 0% incidence of PONV in the PACU between the use of neostigmine-atropine and spontaneous reversal ($p < 0.05$). The authors did not address whether or not groups were similar in regards to menstrual cycle phase. Because the stage of menses has been shown to increase the risk for nausea and vomiting (Honkavarra et al., 1991), it is uncertain whether the study results may have been influenced by the presence of this unmonitored variable. King et al. (1988) observed an 47% versus 11% incidence of PONV between the use of neostigmine-atropine and spontaneous reversal ($p < 0.02$). A weakness of this study is that the authors did not compare groups based on subject gender and age. Although these studies were randomized, the apparent failure to control extraneous variables threaten their internal validity. Their use of neostigmine-atropine limits the clinical significance of their results.

Watcha et al. (1995) observed neostigmine-glycopyrrolate ($n = 38$) to be associated with a significantly greater incidence of PONV in the PACU ($p < 0.05$) when compared with spontaneous reversal (34% versus 11%). The neostigmine-glycopyrrolate group also had a greater need for antiemetic rescue therapy in the

PACU as compared to spontaneous reversal (*n* = 37; 24% vs. 3%; $p < 0.05$).Their use of a sample of children (mean age approximately 9 years old ± 4.0 SD) does not allow the study results to be generalized to adults. Children have known physiologic differences which result in different pharmacokinetics and pharmacodynamics as compared to adults (Stoelting & Miller, 1994). Additionally, patients were distributed among a wide variety of different surgical procedures in this study which may have threatened the study's internal validity. Five different surgical procedures were performed in this study. While increasing the study's generalizability, this may have increased the chance of an extraneous variable (e.g. surgical procedure) influencing the results of the study.

In contrast, Boeke et al. (1994) and Grasela et al. (1994) found no significant difference ($p > .05$) in the incidence of PONV between the use of neostigmine and spontaneous reversal. Boeke et al. studied neostigmine-atropine using a surgical population (*N* = 80) consisting of hernia repair and vein stripping operations. The two types of surgeries were equally distributed in both groups. Although half of the study sample consisted of women, no mention was made of group characteristics regarding menses. It is, thus, not known whether an unmonitored variable may have influenced the results of the study. A further limitation is the study's use of neostigmine-atropine as the reversal modality studied.

Grasela et al. (1994) performed a prospective, observational study (*N* = 5910) across 391 hospitals. Limitations included lack of a standardized anesthesia regime, and no mention of the particular antimuscarinic drug(s) used in combination with

neostigmine. Furthermore, Grasela et al. did not compare the groups regarding gender, age, and other demographic characteristics. With the exception of Boeke et al. (1994), and Grasela et al., the study results cited above suggest neostigmine has emetic actions, and is associated with a greater incidence of PONV than spontaneous reversal.

Edrophonium Versus Spontaneous Reversal

Grasela et al. (1994) observed edrophonium to be associated with significantly less PONV in the PACU (10% versus 13%; $p < .05$) than spontaneous reversal. As mentioned above, limitations included a very limited description of the sample population, lack of a standardized anesthesia protocol, the study's nonrandomized and unblinded nature, and failure of the investigators to indicate which antimuscarinic drug was co-administered with edrophonium. Additionally, no categorization was made according to subject gender, age, or surgical procedure.

To summarize the studies in this section, Kao et al. (1992) and Watcha et al. (1995) observed no significant difference in PONV associated with the use of edrophonium-atropine versus spontaneous reversal. Watcha et al. studied PONV in pediatric patients which prevents the generalization of the results to adult populations. Kao et al., as mentioned above, had low group numbers ($n < 20$) and did not account for menses among their sample population of premenopausal women. These findings from all of the studies above suggest that edrophonium may have a benign or antiemetic effect on the incidence of PONV.

Neostigmine Versus Edrophonium

Several investigators observed neostigmine to be associated with a greater incidence of PONV as compared with edrophonium (Grasela et al., 1994; Kao et al., 1992; Watcha et al., 1995). Grasela et al. observed a 15% versus 10% incidence of emesis in the PACU associated with the use of neostigmine and edrophonium respectively ($p < 0.005$). Kao et al. observed a 37% versus 10% incidence of emesis in the PACU associated with the use of neostigmine and edrophonium respectively ($p < 0.05$). Watcha et. al. observed a 34% versus 18% incidence of PONV in the PACU associated with the use of neostigmine versus edrophonium ($p < 0.05$). As described above, limitations to Grasela et al.'s study included the lack of a standardized anesthesia regime, and a nonrandomized and unblinded design. Further limitations of Grasela et al.'s study included the authors not describing and comparing the groups according to gender, age, surgical procedure, and the particular antimuscarinic drugs used in combination with neostigmine and edrophonium. Limitations of Kao et al.'s study included small sample sizes ($n < 20$), use of neostigmine-atropine, and failure to check for possible differences between groups regarding menstrual status.

Watcha et al. (1995) was the only study found that compared neostigmine-glycopyrrolate with edrophonium-atropine. These investigators observed a significantly greater incidence of emesis between the use of neostigmine-glycopyrrolate and edrophonium-atropine in the PACU (34% vs. 18%; $p < 0.05$). Their use of the recommended reversal combinations gives this study greater clinical relevance than other studies which used neostigmine-atropine (Boeke et al., 1994;

Ding et al., 1994; Huang et al., 1993; Kao et al., 1992; King et al., 1988). Watcha et al.'s use of a pediatric population sample prevents the generalizability of their results to adult patients. As discussed above, children are known to be physiologically different from adults and exhibit differences in drug pharmacokinetics and pharmacodynamics (Stoelting & Miller, 1994).

Contrasting the findings above, Huang et al. (1993) did not observe a significant difference in the incidence of PONV between the use of neostigmine versus edrophonium. Huang et al. (*n* = 50) compared neostigmine-atropine with edrophonium-atropine in a female sample of laparoscopic surgical patients. Although the sample population for Huang et al. consisted entirely of women, no mention was made of menstrual status of the sample population. Because this was not monitored and discussed, it is not known if the study results were influenced by differences in menstrual cycle phases rather than from the use of neostigmine versus edrophonium. Additionally, the use of neostigmine in combination with atropine limits the clinical relevance of the study findings. Within the limitations discussed, study findings suggest that neostigmine is associated with a greater incidence of PONV than edrophonium.

<u>Neostigmine-Atropine versus Neostigmine-Glycopyrrolate</u>

Several investigators observed no significant difference in PONV among neostigmine-atropine and neostigmine-glycopyrrolate (Orko & Rosenberg, 1984; Takkunen, Salmenpera, & Heinonen, 1984). Takkunen et al. found the neostigmine-atropine group to have a statistically significant increased incidence of cardiac

bradyarrhythmias ($p < 0.05$) after reversal of the neuromuscular block. The group receiving neostigmine-atropine experienced a 73% incidence of heart rates < 50 beats per minute ($p < 0.05$) and a 46% incidence of junctional rhythm ($p < 0.05$). The decreased heart rates observed with neostigmine-atropine were not associated with significant changes in blood pressure. Limitations of this study included small group sizes ($n \leq 15$), and no discussion of menses regarding the women in the study.

Orko and Rosenberg (1984) did not study PONV per se, but studied the effects of neostigmine-atropine and neostigmine-edrophonium reversal of neuromuscular block on urinary-bladder function. Both study groups experienced a similar incidence of PONV. The authors additionally reported finding a statistically insignificant higher incidence of postoperative urinary problems in the neostigmine-glycopyrrolate group. The similar incidence of PONV observed may have been influenced by the diversity of surgical procedures performed including intrathoracic, hernia repair, breast surgery, plastic surgery, and laparotomies. Additionally, as with most of the other studies discussed, Orka and Rosenberg did not monitor for or discuss the possible effects of menstrual cycle phase on the incidence of PONV. Due to the limitations discussed, the effect of neostigmine-atropine versus neostigmine-glycopyrrolate on PONV is not clear. The increased incidence of cardiac side effects observed in the presence of neostigmine-atropine supports the use of neostigmine-glycopyrrolate as opposed to the use of neostigmine-atropine (Takkunen et al., 1984). These side effects were well tolerated by the study participants, however junctional rhythms are known to be a

cause of significant circulatory deterioration in patients with hypertension and coronary artery disease (Prys, 1981).

Contrasting the two studies above, Salmenpera, Kuoppamaki, & Salmenpera (1992) observed a statistically significant greater incidence of nausea in the PACU associated with the use of neostigmine-glycopyrrolate versus neostigmine-atropine (28% versus 8%; $p = 0.01$; $n = 50$). The neostigmine-glycopyrrolate group also had a greater incidence of nausea during the first 24 hours after surgery (28% versus 18%; $p = 0.04$). The use of neostigmine-glycopyrrolate was associated with a greater incidence of antiemetic rescue therapy in the PACU ($p = 0.02$). The use of a heterogeneous sample consisting of patients scheduled for hernia repair and vein stripping procedures may have weakened the internal validity of the study. Additionally, Salmenpera et al. used the subjects' inpatient medical records as their data collection tool. The authors admitted that this may have resulted in under reporting the actual incidence of PONV.

A significant limitation of the above three studies was the administration of the antimuscarinic component of the reversal combination both as a premedication prior to anesthesia as well as in combination with the anticholinesterase at the end of the procedure. Premedication with an antimuscarinic medication is not routinely done and may have influenced the incidence of PONV.

Two final criticisms apply to all of the above studies which investigated the incidence of PONV seen with the use of neuromuscular blocker reversal agents. None of these studies monitored the incidence of patient history of motion sickness in each

group. Additionally, none of the studies mentioned the use of a specific PONV data collection instrument or associated reliability and validity testing results.

Summary

PONV is a significant side effect accompanying anesthesia and surgery. Many factors exclusive of anesthesia may put patients at greater risk of this complication.

Present studies lent only weak support for the use of edrophonium rather than neostigmine based on observations showing neostigmine to have been associated with a greater incidence of PONV (Grasela et al., 1994; Kao et al., 1992; Watcha et al., 1995). Only one of the studies discussed above compared neostigmine-glycopyrrolate versus edrophonium-atropine and their associated incidence of PONV (Watcha et al.).

Investigators have observed a significantly increased incidence of PONV associated with the use of neuromuscular reversal agents (mainly with combinations using neostigmine; Ding et al., 1994; Grasela et al., 1994; Kao et al., 1992; King et al., 1988; Watcha et al., 1995). Investigators have also observed a significantly decreased incidence of PONV associated with the use of edrophonium versus neostigmine (Grasela et al.; Kao et al.; Watcha et al.). Current studies of reversal agent effects on PONV are limited by small sample sizes, use of heterogeneous subject populations, and use of neostigmine-atropine as the reversal modality studied. These studies are insufficient to indicate to the anesthesia care provider which of the two recommended agents (i.e. neostigmine-glycopyrrolate versus edrophonium-atropine) is associated with the least incidence of PONV.

CHAPTER III

Methodology

The research design was a prospective, randomized, quasi-experimental, double-blind study using a consecutive sample of adult female volunteers undergoing elective laparoscopic tubal ligation, laparoscopic cholecystectomy, or diagnostic gynecological laparoscopy. The incidence of PONV was compared between the use of neostigmine-glycopyrrolate versus edrophonium-atropine used to reverse neuromuscular block.

The population, sample, setting, instrumentation, procedure for data collection, study design, and data analysis are described. The protection of human subjects, encompassing informed consent, anonymity, privacy, and dissemination of study results will close this chapter.

Population, Sample, and Setting

The sample consisted of women 18 years of age or older who presented for laparoscopic tubal ligation (LTL), laparoscopic cholecystectomy (LC), or diagnostic gynecological laparoscopy (DGL) at a military medical center in the state of Hawaii. A consecutive sample was used due to accessibility and time limitations for this study. Outpatients receiving elective LTL or LC surgery during the time period of November 15, 1996 through May 30, 1997 were considered for inclusion in the study. Outpatients receiving elective DGL surgery during the time period of March 15, 1996 through May 30, 1997 were also considered for inclusion in the study.

Power analysis determined a sample size of 60 subjects per group was needed in order to have an 80% chance to detect a 35% difference at a significance level of 0.05 (Winer, 1971). Due to time constraints and available surgical population, a sample size of only 21 patients in each group was obtained. Because the number of LTL's only averaged about 16/month, it was decided to include outpatient LC's to the sample population. Problems with using this population included: (a) many of these patients were inpatients diagnosed with acute cholecystitis and were admitted to the hospital preoperatively, receiving intravenous fluids and antiemetic medications and (b) many of the outpatients scheduled for LC experienced heart burn as a symptom of their gall-bladder disease necessitating the use of an alternative anesthetic regime. As a result of the above, only 4 LC patients were enrolled into the study. In an effort to increase the study sample size, in March, 1997, DGL's were included in the study. Although this facility performs approximately 220 DGL's per year, many of these diagnostic procedures are performed in conjunction with other surgical procedures such as oopherectomies, ovarian cyst removals, and other procedures which would present possible threats to the internal validity of the study due to the different incidents of PONV associated with these other procedures (Lerman, 1992). Only procedures scheduled as diagnostic laparoscopy (without any accompanying additional surgical procedures) were considered for inclusion in the study. Consequently, only 3 DGL's were entered into the study. It was necessary to complete data collection by May 30, 1997. Due to time constraints and a relatively small number of potential study

subjects, it was not possible to obtain the sample number determined by power analysis.

Patients scheduled for the above procedures were evaluated for study inclusion at least one day prior to surgery. When possible, this was done during their scheduled preoperative interview/assessment. When it was not possible to evaluate patients for inclusion in the study during their preanesthesia visit, patients' medical records were screened for inclusion and exclusion criteria and patients were interviewed by phone.

Inclusion Criteria:

1. English-speaking and reading adult volunteers admitted for elective, outpatient laparoscopic tubal ligation, laparoscopic cholecystectomy, or diagnostic gynecological laparoscopy.

2. American Society of Anesthesiologists (ASA) risk classification Class I or II without emergency qualifier.

3. Surgical procedure duration less than two and one half hours.

Exclusion criteria:

1. History of symptomatic hiatal hernia or frequent complaint of esophageal reflux.

2. Body weight outside of the range of 40-120 kg.

3. Use of antiemetic medications within 24 hours prior to surgery.

4. Patients taking antipsychotic medications.

5. Any condition that precludes proposed perioperative anesthetic plan including allergies to study medications or specific medical conditions which might indicate an alternative anesthetic management plan.

6. Recent cold, within 2 weeks, or current upper-respiratory infection cold or flu with gastrointestinal symptoms.

7. A history of prior PONV defined as nausea and/or vomiting of a duration of greater than one hour.

8. Age younger than 18 or older than 65 years

Potential candidates were identified from the operating room (OR) surgical schedule. The OR schedule was published at least one day in advance. The schedule provided patient names and the date and type of surgery to be performed. The schedule also identified inpatient and outpatient status. Outpatients identified on the schedule were screened for inclusion/exclusion criteria at a minimum of one day prior to their surgery. This was done either during their preoperative assessment interview, by an interview on the phone with the patient, or by reviewing the patient's medical record. Verbal consent was obtained at least one day prior to surgery. Written informed consent was obtained either during the patient's preanesthesia assessment or in the OR holding area on the day of surgery. To ensure that the study was double-blinded, the pharmacist, using a table of random numbers, assigned a study medication of either neostigmine-glycopyrrolate or edrophonium-atropine to the subject. Other than the study medication, the anesthetic regimen was the same for both groups studied. The anesthetic drug dosages were standardized based on a mg/kg dosage where applicable.

The setting for this study was a 537 bed military medical center in a metropolitan area in the state of Hawaii. Patients seen here include military members from all the armed services, their dependents, military retirees, and patients from the

Trust Territories. The main operating room has 13 operating room suites. Approximately 190 laparoscopic tubal ligations, 250 laparoscopic cholecystectomies, and 220 diagnostic gynecological laparoscopies are performed each year. The Department of Pharmacy includes a clinical investigation section and is involved with multiple complex clinical studies. The hospital's Department of Clinical Investigation granted permission to conduct the study (Appendix A).

Instrumentation

Data collection in the hospital consisted of documenting individual episodes of nausea and vomiting, antiemetic and analgesic medications received postoperatively, and time needed to meet PACU and ASC discharge criteria. Starting in the anesthesia holding area, the anesthesia care provider initiated the in-hospital data collection form (Appendix B) annotating demographic data including subject age, ASA category, weight, ethnicity, time in surgery, and days since last menses where applicable. Data collection then occurred in the PACU and continued in the ASC. Nursing personnel in the above areas recorded any incidences of PONV, medications administered to the patient, and the time it took the patient to meet discharge criteria in the PACU and ASC on the in-hospital data collection form (Appendix B).

Data collection upon discharge from the ASC was performed using the Rhodes Index of Nausea and Vomiting (RINV-2) as a self-report form for the patient (Rhodes, Watson, & Johnson, 1984; Appendix C). Data collection ended 12 hours following extubation. The anesthesia care provider contacted the patient by phone the day following the surgery to collect the responses on the RINV-2.

The Rhodes Index of Nausea and Vomiting.

The Rhodes Index of Nausea and Vomiting is an 8-item, 5-point, Likert-type self-report tool (Appendix C). The tool measures patient perception of frequency, duration,

and distress associated with nausea, vomiting, and retching. Scores derived from this tool included scores for symptom occurrence (SO), symptom experience (SE), and symptom distress (SD), as well as a total overall score. Rhodes et al. (1984) have established reliability using Cronbach's alpha (0.89-0.97; $n = 30$) and split-half procedure (0.83-0.99; $n = 25$-32). They have documented the tool's construct validity and criterion-related validity using the Adoptive Symptom Distress Scale. Numerous studies have successfully used the Rhodes Index of Nausea and Vomiting (Jablonski, 1993; O'Brian & Zhou, 1995; Rosecrans et al., 1996; Simms, Rhodes, & Madsen,1993; Stainton, 1994). Because the RINV-2 is a self-report form, patient compliance is essential to ensure the accuracy and completeness of the information. Dr. Verna A. Rhodes granted permission for the use of the RINV-2 for this study (Appendix D).

Instrument Scoring.

The measurement of the incidence of PONV was the total number of patients in each group noted to complain of nausea and/or experience emesis in the OR, PACU, and the ASC. The RINV-2 patient self-report form was used to determine the proportion of study participants experiencing PONV at home. Additionally, RINV-2

subscores were derived which measured patients' perceived symptom occurrence, symptom experience, and symptom distress.

Procedure for Data Collection

The following procedures were used for data collection:

1. Patients identified on the surgical schedule were assessed for enrollment in the study. Patients who met study inclusion criteria were contacted by phone by an investigator at least one day before surgery and asked to participate in the study. When possible, written consent was obtained from patients on the day of their preanesthesia interview in the Preanesthesia Unit (PAU). Otherwise, written, informed consent was obtained on the day of surgery in the operating room holding area.

2. An order was made to pharmacy for study medications one day in advance. Using a sheet of random numbers, a specific pharmacist hired to prepare medication for clinical trials randomly assigned to each patient either neostigmine-glycopyrrolate or edrophonium-atropine.

3. After the arrival of the subject in the OR hold area, written informed consent was obtained (if not already done) and the subject was instructed on the use of the RINV-2 self-report form (Appendix C). The subject was informed that this study would measure aspects of their well-being after surgery. The subject was instructed to record their postoperative experience by reading each row of information on the self-report form and circling the response which best applied to them. The in-hospital data collection form was initiated and demographic data such as age, weight, height, surgical procedure, and menstrual status were recorded. Pharmacy maintained a patient

log that cross referenced patient names and syringe numbers with the drug combination dispensed. This information could be obtained from pharmacy at any time if it became necessary to know which reversal drugs were received by the patient.

4. The patients' chart was labeled with a pink "PONV Study" sticker to indicate participation in this study. An additional sticker was placed under the drip chamber of the patient's intravenous line to further identify the patient as a study participant.

5. Only the investigators, their faculty, and participating pharmacists had access to the patients' names.

6. Pharmacy personnel randomly assigned either study drug to each patient. After preparing the medication, pharmacy personnel added isotonic sodium chloride intravenous solution to each syringe to allow for a total volume of 15 cc. Syringes were identified by patient name, register number, and syringe number.

7. An unblinded faculty preceptor had a copy of the pharmacy code sheet. This allowed the faculty member to quickly determine which drug the patient received in the event of a drug reaction or undesired change in the patient's condition. No adverse reactions or changes in condition were noted. The list was available but not used.

8. Anesthesia and surgical start and end times and time of study drug administration were recorded on the in-hospital data form. All episodes of PONV observed after extubation in the operation room and during the patient's stay in the PACU and ASC were also recorded on this form.

9. Nurses in the PACU and ASC recorded complaints of nausea, incidents of vomiting, analgesic and antiemetic administration, and the time the patient took to meet discharge criteria (Appendix B). All observers were blinded regarding the study medication administered to the patient.

10. Patients were discharged with the RINV-2 to be completed at home.

11. The data collection period ended twelve hours following extubation.

12. An investigator contacted the patient by phone the day after surgery to collect the data on the patient's RINV-2 (Appendix C). All patients had phones and were able to complete the RINV-2 with 100% compliance noted.

Standardized Anesthesia Protocol

1. Lactated Ringers 300-500 cc intravenous fluid preload administered prior to the induction of anesthesia.

2. Midazolam hydrochloride, 1-2 mg, IV administered in the OR holding area.

3. Fentanyl up to 3 mcg/kg IV during induction of anesthesia, and then 1-3 mcg/kg/h as needed for maintenance of anesthesia, not to exceed a total cumulative dose of 7.0 mcg/kg during the entire case.

4. Sodium thiopental 3.0-6.0 mg/kg IV for induction of anesthesia.

5. Vecuronium bromide 0.08-0.1 mg/kg during induction of anesthesia and 0.015 mg/kg IV boluses as needed for maintenance of surgical relaxation as evidenced by 1-2 twitches upon train-of-four stimulation using a peripheral nerve stimulator.

6. Isoflurane inhalation agent 1-2% for maintenance of anesthesia.

7. Oxygen 30-50% intraoperatively and 6-8 liters per minute via face mask postoperatively during transport to the PACU.

8. After induction of anesthesia and intubation of the trachea, an oral gastric tube was placed and the stomach was suctioned per usual institutional protocol for female laparoscopic surgery. At the beginning of laparoscopic surgery, the surgeon inserts a trochar needle blindly into the abdomen in order to insufflate gas and establish a pneumoperitoneum. Suctioning the stomach prevents gastric distention and thereby may decrease the chance of injury upon the insertion of the trochar needle. The oral gastric tube was removed prior to the patient's emergence from anesthesia. A bair hugger was used during maintenance of anesthesia to assist the patient to maintain a normal body temperature.

9. Blinded IV administration of either study drug was done at the end of surgery upon obtaining at least 1-2 twitches upon train-of-four stimulation using a peripheral nerve stimulator:

Group I: Neostigmine 0.06 mg/kg up to a maximum dose of 5 mg with glycopyrrolate 0.02 mg/kg not to exceed a maximum dose of 1 mg.

Group II: Edrophonium 0.9 mg/kg with atropine 0.02 mg/kg.

10. Postoperative pain and PONV in the PACU was treated by the anesthesiologist supervising the PACU. Postoperative pain and PONV occurring in the ASC was treated by the surgeon.

Protection of Human Subjects

Patients were verbally counseled at least one day prior to surgery. Written informed consent was obtained during the patient's preanesthesia interview, when possible, in the PAU or upon the patient's arrival to the OR holding area (Appendix E). It was reinforced to the patient that participation was entirely voluntary and that consent could be withdrawn at any time. The purpose of the research study was explained, and data collection procedures were reviewed. Patients were informed of reasonable risks associated with participating in the study. Anonymity and confidentiality of patient and records were discussed with the patient and the name and phone number of a contact person was provided.

Privacy and anonymity were ensured. Only investigators, selected faculty members, and pharmacy personnel involved in the study had access to patient names and registrar numbers. A patient log which cross referenced patient names and register numbers with syringe number and drug dispensed was maintained by the Pharmacy in a locked file. Patients were informed that information gained from this study may be used as part of a scientific publication in medical or professional journals, but confidentiality would be maintained. Identifying information (patient log) will be destroyed upon final completion of data collection and thesis publication.

Permission to conduct this study was granted by the medical center's Institutional Review Board (Appendix A), the Human Use Committee, and the Committee for the Protection of Human Subjects (CPHS) at The University of Texas at Houston Health Science Center (page iv).

Study Design

The research design was a quasi-experimental, double-blind study designed to compare the incidence of PONV with the drug combinations of edrophonium and atropine versus neostigmine and glycopyrrolate. The subjects consisted of a consecutive sample of women undergoing laparoscopic procedures randomly assigned to one of the two treatment groups.

Internal and External Validity

Internal validity asks whether the independent variable, in this case the drug combination, is the deciding factor for the outcome of the study. One threat to internal validity included selection bias. Selection bias may occur when subjects are screened to determine those who fit the selection criteria. The use of standardized inclusion and exclusion criteria decreased the chance for selection bias. Additionally, demographic factors which may confound results by predisposing a person to PONV, such as age, menstrual cycle phase, obesity, or a history of previous episodes of PONV were noted and compared across both groups. Internal validity was also threatened by the occasional implementation of the standardized anesthesia protocol by staff anesthesia care providers who were not otherwise involved in this study. This threat to internal validity was addressed by informing all anesthesia care providers orally and in writing of the anesthesia protocol the day prior to giving the anesthetic. The varying levels of proficiency among anesthesia and surgical residents may also have influenced the incidence of PONV and, thus, threatened the study's internal validity. New surgical residents begin their clinical practicum in July while new nursing anesthesia residents

begin their clinicals in September. It is possible that by starting the study in the middle of November, experience related variables may have been minimized.

Potential threats associated with instrumentation included the use of multiple observers who completed the patient data collection tool. Different nurses caring for the patient in the PACU and the ASC recorded the occurrence and intensity of PONV. The potential arises for differing subjective perceptions of the patients and nursing staff as to what "nausea" and "retching" means to them. PACU and ASC personnel were briefed with oral and written instructions. Data forms were monitored on a weekly basis for compliance with instructions. Discrepancies were discussed with PACU or ASC staff members when appropriate to ensure consistency in data collection.

External validity asks whether the independent variable would produce the same results in another population or setting as the results that were seen here. The largely military population served by this hospital in this overseas location may be significantly different from a population of patients seen at an urban mainland U.S. hospital. It is possible that different results might be obtained if the same treatment was administered in such a setting. Because the surgical procedures in this study were limited to elective laparoscopic surgical procedures in women, the findings may only be generalizable to this population.

Data Analysis

The student's t-test was used to examine the demographic data in each group to determine if significant differences existed between the two groups. One-way

ANOVA was used to analyze continuous data. Due to the small group sizes in this study ($n = 21$), Fisher's exact test was used to evaluate nominative data regarding the proportional incidence of PONV seen between the two groups. Pearson's r was used to look for correlations among the data. A difference was considered significant at $p < 0.05$. Data analysis was performed by an investigator using Statistical Products and Solutions Software (SPSS), version 7.0 (1996). A statistician reviewed the analysis methodology for correctness and accuracy.

Chapter IV

Analysis of the Data

The purpose of this study was to compare the incidence of postoperative nausea and vomiting (PONV) observed with the use of neostigmine-glycopyrrolate versus edrophonium-atropine. In this chapter, both study groups are compared regarding demographic characteristics and study findings. Study findings support the null hypothesis: There is no difference in the incidence of PONV following elective laparoscopic surgery in women when a reversal dose of neostigmine-glycopyrrolate or edrophonium-atropine is used.

Description of the Sample

The consecutive sample consisted of 42 ASA I or II women scheduled for laparoscopic surgery (tubal ligation, cholecystectomy, or diagnostic gynecological laparoscopy). Sixty-seven patients were initially enrolled. Twenty-five of these patients were subsequently disenrolled from the study (Table 1). Protocol violations constituted the major cause of patient removal from the study. In eight instances, it was necessary to deviate from the standardized anesthesia protocol due to patient conditions such as asthma, significant episodes of hypertension, patient history of latex allergy, risk factors for aspiration, or slow wake-up from anesthesia requiring the use of naloxone. Twelve patients were removed from the study due to unintentional protocol violations. These consisted of (a) five instances of nitrous oxide use during maintenance, (b) three instances of exceeding the protocol dose range of sodium

thiopental, (c) three instances of exceeding the dose range of fentanyl, and (d) one instance of giving midazolam to a patient without first obtaining written consent.

In two cases, ketorolac was given intraoperatively, once in Group I and once in Group II. Ketorolac is a nonsteroidal antiinflammatory drug often administered at the end of female gynecological surgical procedures for the control of postoperative pain. The two instances of intraoperative ketorolac use were considered minor protocol violations which had occurred equally in both groups. Accordingly, it was decided to allow these two patients to remain in the study. Data analysis was performed with and without these two patients without a change in study findings. Thirty-one patients were not enrolled in the study due to exclusion criteria (Table 2).

Table 1

Patients Disenrolled From The Study ($n = 31$)

Reason for disenrollment	Frequency
Unintentional deviation from study protocol	12
Protocol deviation due to medical safety	8
Cancellation of surgery	3
Surgery time greater than 2.5 hours	1
Last minute decision by patient not to be in study	1
Total	25

Pharmacy personnel using a randomization table, randomly assigned patients to Group I (neostigmine-glycopyrrolate) or Group II (edrophonium-atropine). All investigators and observers were blinded regarding the identity of the study drug given the patient. Both groups were equal in size with 21 patients assigned to each group.

Table 2

Patients Not Enrolled In Study ($n = 31$)

Exclusion criteria for patients not enrolled in study	Frequency
Known risk for pulmonary aspiration	8
Care provider other than investigators doing the case[a]	8
Current medication use associated with PONV	7
Patient refusal	4
Morbid obesity (more than twice ideal body weight)	3
Family history of malignant hyperthermia	1
Total	31

[a]In 8 cases, patients were removed from the study when an anesthetist assigned do the case (and not otherwise involved in the study) declined to implement the standardized study protocol.

Both groups were similar with respect to demographic characteristics (Table 3). There were no significant difference in subject age, body mass index (BMI), military status, race, or phase of menstrual cycle between the two groups (Table 3).

Table 3

Demographic Data Comparing the Two Groups in the PONV Study ($N = 42$)

Demographic data	Group I ($n = 21$)	Group II ($n = 21$)	Probability
Age (yr)	26.6 ± 4.3	28.8 ± 4.5	0.42
Body mass index	23.6 ± 3.2	24.9 ± 2.3	0.14
History of motion sickness	3 (14%)	1 (5%)	0.25
Military active duty	10 (48%)	5 (24%)	0.11
Civilian	11 (52%)	16 (76%)	0.11
White	14 (66%)	15 (71%)	1.00
Black	4 (19%)	3 (14%)	1.00
Hispanic	1 (5%)	2 (9%)	0.73
Asian	2 (9%)	1 (5%)	0.73
Menstrual phase:			
Preovulatory (days 1-8)	4 (19%)	6 (28%)	0.76
Ovulatory (days 9-16)	2 (9%)	2 (9%)	1.00
Postovulatory (days 17 till end)	11 (52%)	7 (38%)	0.51
Postmenopausal and others	4 (19%)	6 (28%)	0.76

Note: Values for continuous data are mean plus or minus standard deviation. Numbers with percentages refer to number of subjects and the percent of the group they constitute.

Anesthetic and surgical variables were also similar between the two groups (Table 4). There was no significant difference in subject American Society of Anesthesiologists (ASA) classification, anesthetic drug doses administered, type of surgery, or anesthesia and surgery times. The incidence of use of postoperative opioids for pain control was also similar for the two groups (Table 5). Antiemetic rescue therapy used in both groups is shown in Table 5. Demographic and anesthesia and surgical characteristics were evaluated with the Student's t test and were not found to be statistically significant.

Findings

Primary Data Analysis

Both groups were observed in the OR, PACU, and ASC for incidents of nausea, emesis, need for antiemetic rescue therapy (Table 6) and time until ready for discharge from the PACU and ASC (Table 7). The RINV-2 was used by the patient to record PONV symptom occurrence (SO), symptom distress (SD) , and symptom experience (SE) occurring from the time of discharge from the ASC until twelve hours after extubation. The mean RINV-2 scores for each group, total range of scores possible, and probabilities are shown in Table 8. One-way ANOVA was used to correlate the incidences of PONV, PACU and ASC recovery times, and the RINV-2 scores to the reversal drug given. The proportion of patients in each group experiencing PONV and the proportion of patients receiving antiemetic rescue therapy was evaluated with Fisher's exact test. This test was chosen rather than Chi Square due to the relatively low sample sizes in this study. Continuous data was examined with

Pearson's r to determine the existence of significant correlations between data. The level of significance chosen for this study was $p < 0.05$.

Table 4

Anesthetic and Surgical Variables

Variables	Group I ($n = 21$)	Group II ($n = 21$)	Probability
ASA I	15 (71%)	12 (57%)	0.52
ASA II	6 (28%)	9 (43%)	0.52
Anesthesia time (minutes)	112.1 ± 28.4	110.5 ± 23.2	0.84
Surgical time (minutes)	38.9 ± 24.6	47.0 ± 28.0	0.32
Total dose of thiopental (mg/kg)	4.5 ± 0.5	4.6 ± 0.8	0.58
Total dose of fentanyl (ug/kg/h)	2.07 ± 0.63	2.11 ± 0.73	0.84
Laparoscopic tubal ligation	17 (81%)	18 (86%)	1.00
Laparoscopic cholecystectomy	2 (9%)	2 (9%)	1.00
Diagnostic laparoscopy	2 (9%)	1 (5%)	0.73

Note: Values for continuous data are mean plus or minus standard deviation. Numbers with percentages refer to number of subjects and the percent of the group they constitute.

Table 5

Postoperative Use of Analgesic and Antiemetic Medications

Medication	Group I ($n = 21$)	Group II ($n = 21$)	Probability
Pain medications			
Morphine sulfate	11 (52%)	9 (43%)	0.63
Meperidine sulfate	2 (9%)	1 (5%)	0.73
Other opioid use	3 (14%)	2 (9%)	0.64
Ketorolac	5 (24%)	8 (38%)	0.19
Antiemetic medications			
Droperidol	2 (9%)	0 (0%)	0.15
Ondansetron	3 (14%)	2 (9%)	0.64
Other	1 (5%)	1 (5%)	1.00

Note: Numbers and percentages refer to number of subjects who received particular medications and the percent of the group they constitute.

Table 6

Incidence of PONV By Location of Patients at Time of Incident

Location	Group I ($n = 21$)	Group II ($n = 21$)	Probability
OR:			
Nausea	0 (0%)	1 (5%)	1.00
Emesis	0 (0%)	1 (5%)	1.00
Total PONV[a]	0 (0%)	2 (9%)	0.48
Rescue therapy	0 (0%)	0 (0%)	1.00
PACU:			
Nausea	5 (24%)	2 (9%)	0.41
Emesis	2 (9%)	0 (0%)	0.48
Total PONV[a]	5 (24%)	2 (9%)	0.41
Rescue therapy	4 (19%)	1 (5%)	0.18
ASC:			
Nausea	9 (43%)	8 (38%)	1.00
Emesis	7 (33%)	6 (28%)	0.75
Total PONV[a]	13 (61%)	9 (43%)	0.18
Rescue therapy	1 (5%)	2 (9%)	1.00

Note: Numbers with percentages refer to number of subjects and the percent of the group they constitute. [a] Total PONV refers to the number and percentage of subjects experiencing either nausea and/or emesis.

table continues

Table 6

Incidence of PONV By Location of Patients at Time of Incident

Location	Group I ($n = 21$)	Group II ($n = 21$)	Probability
Home:			
Nausea	10 (48%)	11 (52%)	1.00
Emesis	9 (43%)	9 (43%)	1.00
Total PONV[a]	12 (57%)	12 (57%)	1.00

Note: Numbers with percentages refer to number of subjects and the percent of the group they constitute. [a] Total PONV refers to the number and percentage of subjects experiencing either nausea and/or emesis.

Table 7

Discharge Times From PACU and ASC

Location	Group I ($n = 21$)	Group II ($n = 21$)	Probability
PACU (minutes)	71.6 ± 36.4	63.0 ± 23.3	0.37
ASC (minutes)	$156.9 + 77.8$	$110.7 + 59.4$	0.04

Note: Values are mean plus or minus standard deviation.

PONV Observed in the OR

The incidence of PONV seen here between Group I and II (0% versus 9 %) was not statistically significant ($p = 0.48$).

PONV Observed in the PACU

A greater percentage of the patients in Group I (neostigmine-glycopyrrolate) were observed to have incidences of nausea (24% vs. 9%; $p = 0.41$), emesis (9% vs. 0%; $p = 0.48$), total episodes of PONV (24% vs. 9%; $p = 0.41$) and rescue therapy (19% vs. 5%; $p = 0.18$) which were all statistically insignificant. Group I's time to meet PACU discharge criteria was longer on average by 9 minutes ($p = 0.37$).

PONV Observed in the ASC

Subjects in Group I were again observed to have greater (though statistically insignificant) incidences of PONV as compared with Group II (61% versus 43%; $p = 0.185$). Patients in Group I took an average of 157 minutes to meet ASC discharge criteria compared with 111 minutes for Group II. This was an average difference of 46 minutes which was statistically as well as clinically significant ($p = 0.04$). The incidence of antiemetic rescue therapy was the similar for both groups ($p = 1.00$).

PONV After Discharge From the Hospital

Fifty-nine percent of the subjects in each group experienced an incident of PONV at home. RINV-2 scores between groups were not statistically significant (Table 8). Both groups reported similar scores regarding their perceived level of

Table 8

RINV-2 Score Means Compared to Total Scores Possible

Score	Group I	Group II	Possible range of scores	Probability
SO-Nausea	1.8 ± 2.3	1.6 ± 2.2	0-8	0.79
SO-Emesis	1.0 ± 1.6	1.5 ± 2.1	0-8	0.46
SO-Retching	0.2 ± 0.4	0.1 ± 0.3	0-4	0.68
SO-Total	3.1 ± 3.5	3.3 ± 3.9	0-20	0.81
SE-Nausea	2.1 ± 2.7	2.4 ± 3.1	0-12	0.75
SE-Emesis	1.5 ± 2.2	2.1 ± 3.0	0-12	0.42
SE-Retching	0.4 ± 0.9	0.4 ± 1.0	0-8	0.87
SE-Total	4.0 ± 5	5.0 ± 6.1	0-32	0.58
SD-Nausea	0.5 ± 0.6	0.7 ± 0.8	0-4	0.40
SD-Emesis	0.5 ± 0.9	0.6 ± 1.1	0-4	0.76
SD-Retching	0.2 ± 0.5	0.2 ± 0.7	0-4	1.00
SD-Total	1.2 ± 1.5	1.5 ± 2.1	0-12	0.62
RINV-Total	4.04 ± 4.8	4.9 ± 6.1	0-64	0.59

Note: Data listed under columns Group I and Group II are mean ± standard deviation.

distress, symptom experience, and symptom occurrence. Group means listed in Table 8 show low RINV-2 scores relative to the potential range of scores. Large standard deviations indicated considerable variation within each group. The overall low scores for symptom occurrence, symptom distress, and symptom experience suggest most patients perceived their PONV episodes as mild. No patients were admitted to the hospital due to PONV, and no patients experienced significant PONV requiring them to return to the hospital for treatment. All patients were able to complete the RINV-2 and provide the scores to an investigator upon telephonic follow-up on the day following surgery.

Total group percentages of subjects experiencing any incidence of PONV for the entire period monitored were 71% and 66% ($p = 1.0$) for Groups I and II respectively. The total incidence of PONV for both groups combined was 69%.

Summary of Primary Data Analysis

The incidence of PONV, rescue therapy use, and RINV-2 scores were not observed to be statistically different between the two groups. Accordingly, the null hypothesis is accepted and it is concluded that no difference was observed in the incidence of PONV between the use of neostigmine-glycopyrrolate and edrophonium-atropine when used as reversal agents for female laparoscopic surgery patients.

Group I experienced a greater incidence of PONV in the PACU ($p = 0.41$) and the ASC ($p = 0.35$), but it was statistically insignificant. Group I also experienced a greater incidence of rescue therapy use in the PACU which was also statistically

insignificant ($p = 0.18$). Subjects in Group I were noted to spend an average of 46 minutes longer than subjects in Group II to meet ASC discharge criteria ($p = 0.04$).

As noted in Chapter III, a power analysis indicated the need for 60 subjects in each group in order to have a 0.80 chance of detecting a 35% difference at a significance level of 0.05. Statistically increasing the sample size to $N = 120$ changed the level of significance obtained. Expanding the sample size caused the significance levels to increase for PONV in the PACU (from $p = 0.41$ to $p = 0.05$) and for PONV in the ASC (from $p = 0.35$ to $p = 0.15$). The incidence of PACU rescue therapy level of significance increased from $p = 0.18$ to $p = 0.04$ after expansion of the sample size. The relatively small sample size in this study and the change in the level of significance seen upon statistically increasing the sample size suggest the possibility of a Type II error.

Data Analysis of the Combined Demographic Data

Demographic data analysis was performed using one-way ANOVA and Pearson's r to evaluate the possible correlation between demographic factors and the observed incidence of PONV.

Motion Sickness

Four patients in the study had a history of motion sickness. Motion sickness was significantly correlated with emesis in the ASC ($p < 0.05$). The correlation between motion sickness and rescue medication use in the PACU also reached significance ($p = 0.05$). Two of these patients experienced PONV in the PACU (50%, $p < 0.05$) and required rescue therapy. All four patients with a history of motion

sickness (100%) experienced PONV in the ASC but did not require rescue therapy. Two of the patients (50%) experienced PONV at home. Motion sickness did not significantly correlate with other variables such as time to meet discharge criteria in the PACU and ASC or RINV-2 scores.

<u>Body Mass Index</u>

There was a negative correlation between BMI and time to meet ASC discharge criteria (p=0.02). No correlation was observed between BMI and incidences of PONV.

<u>Anesthesia Time</u>

Anesthesia time correlated positively with the incidence of emesis occurring after discharge from the ASC ($p = 0.002$) and correlated positively with RINV-2 scores for SD-total ($p = 0.03$). Positive correlations were also observed between anesthesia time and need for antiemetic rescue in the PACU ($p = 0.02$) and total overall need for rescue throughout the hospital stay ($p = 0.02$).

<u>Surgical Time</u>

Surgical time was positively correlated with nausea in the PACU ($p = 0.03$), total PONV in the PACU ($p = 0.01$), antiemetic use in the PACU ($p = 0.002$), overall incidence of antiemetic rescue use in the hospital ($p = 0.03$), and patients' RINV-2 score for SD-retching ($p = 0.01$).

<u>Age</u>

Age was negatively correlated with the incidence of nausea in the PACU ($p = 0.05$).

Intraoperative Anesthesia Medications

There was a negative correlation between the amount of fentanyl administered intraoperatively and the incidents of emesis after discharge from the ASC ($p = 0.02$). Negative correlation was also seen with the amount of fentanyl use and the patients' RINV-2 SD-emesis scores. In several instances, negative correlations were observed that approached but did not reach statistical significance: nausea in the PACU ($p = 0.07$), emesis in the ASC ($p = 0.07$), total incidence of emesis ($p = 0.06$), and time to meet ASC discharge criteria ($p = 0.09$).

Postoperative Analgesia Medication

Morphine use was positively correlated with total incidents of emesis ($p = 0.03$), incidents of emesis after discharge from the ASC ($p = 0.01$), PACU recovery time ($p = 0.05$), and RINV-2 scores for SE-emesis ($p = 0.01$), and SO-emesis ($p = 0.007$). No correlations were found between the use of meperidine or ketorolac in this study and the incidence of PONV.

Race

Asian race was positively correlated with emesis incidence in the PACU ($p = 0.01$) and ASC ($p = 0.001$) and need for antiemetic rescue therapy in the PACU ($p = 0.01$) and overall incidence of rescue therapy ($p = 0.03$). All Asian patients ($n = 3$) experienced PONV. It was also noted that of the three Asian subjects, two had a history of motion sickness.

Hispanic race ($n = 3$) was also positively correlated with antiemetic rescue therapy in the PACU ($p = 0.02$). The correlations observed between Asian and

Hispanic race and PONV are weakened by the small numbers of such patients in this study. No other significant correlations were observed between subject race and the incidence of PONV.

Other Study Variables

Other variables including subject menstrual cycle status, BMI, ASA classification, and military status (active duty versus civilian) did not significantly correlate with the incidence of PONV in this study.

Summary

Student's *t* testing showed both groups to be similar in their demographic characteristics. No significant difference in the incidence of PONV was observed between the two groups. Group I took significantly longer (46 minutes) to meet ASC discharge criteria ($p = 0.04$). Group I was also observed to have a greater incidence of PONV in the PACU and ASC which was not statistically significant but became so upon statistically increasing the sample size up to 120 (the number needed according to power analysis). The incidence of PONV was also observed to increase for both groups with the passage of time with the highest incidences of PONV being observed in the ASC and at home (52% and 57% respectively). Because of the small sample size relative to power analysis (42 vs. 120), a Type II error can not be ruled out.

Demographic data analysis showed significant correlations between age, motion sickness, intraoperative anesthetic use, postoperative analgesic use, surgical and anesthesia times and the incidence of PONV. Findings also suggested that Asian and Hispanic race may be associated with greater incidences of PONV.

CHAPTER V

Discussion, Conclusions, Implications, and Recommendations

Postoperative nausea and vomiting (PONV) are serious side effects of anesthesia and surgery. PONV are two of the most frequent causes of unanticipated hospital admissions, extended anesthesia recovery time and increased cost of care (Carroll et al., 1994). Metter et al. (1987) found that PONV occurrence rates ranged from 25% to 45% following laparoscopic procedures, with the variance depending on the anesthetic technique. Clinical evidence implicates neuromuscular blocker reversal agents as causes of PONV (Ding et al., 1994; Grasela et al., 1994; Kao, et al., 1992; King et al., 1988; Watcha et al., 1995). The goal of this study has been to compare the incidence of PONV associated with the use of neostigmine-glycopyrrolate versus edrophonium-atropine to reverse neuromuscular block.

Neostigmine-glycopyrrolate and edrophonium-atropine are the two drug combinations currently used and recommended to reverse neuromuscular blockade. Many studies, however, have examined the effects of less suitable anticholinesterase-antimuscarinic combinations, such as neostigmine-atropine (Boeke et al., 1994; Huang et al., 1993; Kao et al., 1992; King et al., 1988). No adult clinical studies were found comparing the incidence of PONV seen between the use of neostigmine-glycopyrrolate versus edrophonium-atropine.

This chapter provides a discussion of the study results observed in the OR, PACU, ASC, and at home. Factors other than the study reversal agents which may

have influenced the incidence of PONV in this study are also discussed. Conclusions supported by data findings are then provided. Finally, nursing implications and recommendations for future research are presented.

Discussion

Study findings support the null hypothesis. No statistically significant difference was observed in the incidence of PONV associated with the reversal of neuromuscular blockade using neostigmine-glycopyrrolate versus edrophonium-atropine on women undergoing laparoscopic tubal ligation, diagnostic gynecologic laparoscopy, or laparoscopic cholecystectomy. Findings are discussed in relation to theory and the literature.

Findings Relative to the Theoretical Framework and Literature

PONV is the end result of a multifactorial process associated with surgery and anesthesia. Variables affecting PONV may be specific to the patient, the surgery, the anesthetic, or the postoperative period. Stimulation of the chemoreceptor trigger zone (CTZ) and activation of the vomiting center (VC) can occur simultaneously by stimulation from medications and surgery during the intraoperative period (Borison & Wang, 1953; Brunton, 1996). Preexisting conditions such as motion sickness can also predispose patients to PONV (Andrews, 1992; Lerman, 1922; Rosecrans et al., 1996). To single out one factor as the paramount cause of PONV would be erroneous. PONV results from the stimulation of a complex process that involves the coordination of input from many areas of the brain and gastrointestinal tract (Andrews; Lerman).

No statistically significant difference in the incidence of PONV or antiemetic rescue therapy use was observed between the use of neostigmine-glycopyrrolate versus edrophonium-atropine to reverse neuromuscular blockade after selected laparoscopic surgical procedures. Specific results observed in the OR, PACU, ASC, and at home are discussed relative to theory and findings in the literature.

PONV in the OR

In the OR, patients in Group II experienced a statistically insignificant greater incidence of PONV (9% versus 0%; $p = 0.48$). No rescue therapy was administered in either group. Antiemetics may not have been given due to the short time interval between extubation and admission to PACU.

An early incidence of PONV as seen in the edrophonium-atropine group might be attributable to the faster onset of edrophonium (<1 minute) rather than neostigmine (2-3 minutes). Edrophonium may also have a slightly faster onset than atropine (30 vs. 45 seconds). Edrophonium could cause PONV shortly after its administration due to muscarinic stimulation that is briefly unopposed by atropine. Unopposed muscarinic stimulation of the stomach can result in gastric spasms. Gastric spasms result in increased afferent vagal nervous stimuli to the vomiting center predisposing the patient to have PONV (Andrews, 1992). Because the difference in PONV between the two groups was not statistically significant, the difference observed is presumed to have occurred by chance rather than due to the specific reversal agent given.

PONV in PACU

In the PACU, patients in Group I experienced statistically insignificant greater incidences of nausea (24% versus 9%, $p = 0.41$), vomiting (9% versus 0%, $p = 0.48$), total PONV (24% versus 9%, $p = 0.41$), and rescue therapy use (19% versus 5%, $p = 0.18$). Contrasting these findings, several investigators have observed neostigmine to be associated with a statistically significant greater incidence of PONV than edrophonium (Grasela et al., 1994; Kao et al., 1992; Watcha et al., 1995). Neostigmine's potent antimuscarinic effects, especially in the gastrointestinal tract, are blamed for its emetic effect (Stoelting, 1991). Its relatively short half-life of 1-2 hours (Stoelting) make its emetic effect most likely to be seen in the immediate postoperative period.

Atropine, unlike glycopyrrolate, is able to cross the blood-brain barrier and exert central effects. Atropine is believed to have an antiemetic effect in the brain by blocking the transmission of central cholinergic impulses to the vomiting center (Mirakhur & Dundee, 1981; Stoelting, 1991). Glycopyrrolate has not been observed to have an antiemetic effect. Accordingly, edrophonium-atropine might be expected to be associated with a lesser incidence of PONV than neostigmine-glycopyrrolate.

Each of the agents used in both reversal combinations should have achieved peak effect at this time; edrophonium 1-5 minutes, neostigmine 3-14 minutes (Savarese et al., 1994). Therefore, the strongest effect of all four agents administered should start to be seen at this time in the PACU, and continue in the ASC.

Although Group I experienced a greater incidence of nausea, emesis, and rescue therapy in the PACU, the difference between the two groups was not statistically significant. Therefore, the difference is presumed to have occurred by chance. Alternatively, the lack of statistical significance might reflect the possibility of a Type II error. Statistically expanding the study sample size to $N = 120$ (the number of subjects needed according to power analysis) changed the significance levels for PONV in the PACU from $p = 0.41$ to $p = 0.05$ and for PACU rescue therapy use from $p = 0.18$ to $p = 0.04$. Thus, it is possible that there were too few subjects in this study to demonstrate a statistically significant difference.

Variables other than the specific reversal agent given were found to correlate with the incidence of PONV observed in the PACU. Factors that were positively correlated with PONV and rescue therapy in the PACU included (a) patient history of motion sickness and rescue therapy ($p < 0.05$), (b) surgical time and nausea ($p = 0.03$), (c) morphine use and nausea ($p = 0.03$), (d) Asian race and emesis ($p = 0.01$) and need for rescue therapy ($p = 0.03$), and (e) Hispanic race and antiemetic rescue therapy ($p = 0.02$).

Negative correlations in the PACU included (a) age and nausea ($p = 0.05$), and (b) fentanyl and nausea ($p = 0.07$). The above listed variables were represented similarly among the two groups. It is, therefore, unlikely that these factors exerted an unequal effect on either group. These and other factors which influenced the incidence of PONV and rescue therapy use are discussed later in this chapter.

Group I's time to meet PACU discharge criteria was longer than Group II's on an average of 7.6 minutes (71.6 minutes versus 63.0 minutes; $p = 0.37$). No correlation was shown between the incidence of PONV and the time needed to meet PACU discharge criteria. Factors which might account for a longer time to meet PACU discharge criteria include (a) inadequate pain control, (b), slower time to awakening and orientation, or (c) inadequate respiratory, circulation, and activity scores as evaluated by the PACU nursing staff. The difference in PACU time to meet discharge criteria between the two groups was not statistically significant and may have been due to chance. No correlation existed between the incidence of PONV and the time to meet PACU discharge criteria.

Adequate use of fentanyl intraoperatively may have allowed patients to rest relatively pain-free at this time, balancing the continuum between pain and PONV with opioid use. Adequate use of intraoperative fentanyl could have also decreased the need for postoperative morphine, with its known emetic properties. Patients experiencing pain have greater circulating levels of catecholamines which stimulate the CTZ and result in PONV (Andrews 1992; Lerman, 1992). Administration of opioid analgesics has been observed to relieve nausea (Andersen & Krohg, 1976). Congruent with the results in this study, Claxton, McGuire, Chung, & Cruise (1997) observed the use of fentanyl to be associated with a decreased incidence of PONV postdischarge as compared to the use of morphine.

PONV in the ASC

Group I again experienced a statistically insignificant greater incidence of PONV in the ASC as compared with Group II (63% vs 43%, $p = 0.185$). As discussed in the section above, results in the literature suggest that neostigmine is associated with a significantly greater incidence of PONV than edrophonium. No adult clinical studies were found comparing neostigmine-glycopyrrolate with edrophonium-atropine. Because the antimuscarinic and the muscarinic component of both reversal combinations have similar onsets and durations, similar side effect profiles might be expected. The higher incidence of PONV observed with neostigmine-atropine versus edrophonium-atropine (Kao et al., 1992) may reflect the difference in onset and duration between neostigmine and atropine. The higher incidence of PONV observed in Group I was not statistically significant and was presumed to be due to chance and not due to a greater emetic effect of neostigmine-glycopyrrolate.

There was no difference between the two groups regarding the incidence of antiemetic rescue therapy use in the ASC. During the first several months of this study ASC policy did not allow ASC nurses to administer parenteral antiemetics. The only antiemetics available during this period consisted of rectal suppositories. It is not known if this may have influenced patients' acceptance of an offered antiemetic. This may have been responsible for the low 7% incidence of antiemetic use seen across both groups.

A Type II error is possible due to the small sample sizes in this study. However, when the sample size was statistically increased to 120, the incidence of PONV and rescue therapy use in the ASC did not reach statistical significance.

Factors that showed a positive correlation for emesis in the ASC included history of motion sickness and Asian race. Two of the three subjects from the Asian Group also had a history of motion sickness.

Body mass index (BMI) showed a negative correlation with the time to meet ASC discharge criteria ($p = 0.02$). Investigators have noted a positive correlation between obesity and PONV (Andrews, 1992; Lerman, 1992). This would presumably lead to delayed readiness for discharge. This study, however, avoided extremes of weight. It is not known why increased weight negatively correlated with time to meet discharge criteria in this study.

The negative correlation between the amount of fentanyl given intraoperatively and emesis in the ASC approached significance ($p = 0.07$). Similar findings were observed by Anderson and Krohg (1976) who found that administration of an opioid to relieve postoperative pain was followed by relief of nausea. Patients experiencing pain have a greater circulating level of catecholamines which stimulate the CTZ and result in PONV.

Patients in Group I took an average of 157 minutes to meet ASC discharge criteria compared with 111 minutes for Group II. This was an average difference of 46 minutes which was statistically significant ($p = 0.04$). The ASC nurses were interviewed in an attempt to explain the delay in patient discharge. The ASC nurses

identified usual problems which often delay discharge from the ASC including (a) inability to void, (b) inability to drink 120 cc of water or apple juice without experiencing PONV, (c) unsteady gait, (d) uncontrolled pain, and (e) dizziness upon standing. All ASC forms were examined, but did not identify specific reasons for the prolonged time to meet discharge criteria seen with Group I. No correlation existed between the incidence of PONV in this study and time to meet ASC discharge criteria. Other factors such as ability to void, and dizziness upon standing which might have explained the difference between the two groups were not monitored. It is, thus, not known why Group I took 46 minutes longer on average to meet ASC discharge criteria. Urinary retention due to anticholinergic drugs such as atropine and glycopyrrolate is one possibility which is discussed in a following section.

PONV at Home

Both groups reported a 59% incidence of PONV at home. Rhodes INV scores were not significantly different between the two groups. Both groups reported similar scores regarding their perceived level of distress, symptom experience, and symptom occurrence. Considering the relatively short half-life of all reversal agents used, it is not surprising that the incidence of PONV at home would be similar. Anesthesia time and morphine use was positively correlated with emesis and Rhodes INV-2 scores during this period.

Investigators in this study did not monitor or attempt to control variables such as postdischarge pain medication use, travel method and time, and activity at home. Oral home pain medication, ambulation, intake of fluids, availability of a restful

environment, and turbulent or prolonged travel home are suspected of influencing the occurrence of PONV (Andrews, 1992; Lerman, 1992; P. Nishimoto, personal communication, July 7, 1997). Because of the randomized nature of this study, these postoperative factors are assumed to have been similar in both groups.

Total PONV

Total incidences of PONV for the entire period monitored were 71% and 66% for Groups I and II respectively ($p = 1.0$). Additionally, no statistically significant difference was observed in patients' RINV-2 scores. Accordingly, it is concluded that there was no difference in the observed incidence of PONV between the use of neostigmine-glycopyrrolate versus edrophonium-atropine.

The physiologic effect of reversal agents would be expected to wane during the first 1 - 4 hours after their administration consistent with their relatively short half-lives. Accordingly, a difference in PONV would probably be seen mainly during the immediate postoperative period. Patient, anesthetic, surgical, and postoperative factors which may have influenced the incidence of PONV in this study are now discussed.

Patient related factors

As discussed in Chapter II, many factors having nothing to do with the surgery or anesthetic may influence the occurrence of PONV. Patient related factors that significantly correlated with PONV in this study included age, gender, motion sickness, and race. Both groups were similar regarding these demographic characteristics.

Variables including menstrual cycle phase, BMI, ASA classification, and military status did not significantly correlate with the incidence of PONV. Demographic, surgical, and anesthetic factors which may have influenced the incidence of PONV observed in this study are discussed below.

1. Age: The age range for this study, 22 to 39 years, represents roughly the second quarter of the human life-span. This age group well represented the majority of patients that would present for laparoscopic surgery. In this study, age was negatively correlated with the incidence of nausea in the PACU ($p = 0.05$). This result is consistent with findings in the literature which show a decreased incidence of PONV with increasing age (Cohen et al., 1994; Lerman, 1992).

2. Gender: All subjects were female. Women are reported to have a 2-3 fold increase in PONV when compared to men (Andrews, 1992; Lerman, 1992). As discussed in Chapter II, disagreements exist in the literature regarding which phase of the menstrual cycle may be associated with a greater incidence of PONV. This study found no significant correlation between menstrual cycle phase and the incidence of PONV. This finding is consistent with observations made by Gratz et al.(1996) and Rosecrans et al. (1996) who also did not find a relationship between the incidence of PONV and the phase of the menstrual cycle. Andrews (1992) and Lerman (1992) reported significant differences in the incidence of PONV depending on the phase of the menstrual cycle. The reason for the conflicting results in the literature is not clear. Investigators in both this study ($N = 42$) and the study by Rosecrans et al. ($N = 46$)

enrolled a relatively small number of subjects which may have been insufficient to statistically show a significant difference.

3. Obesity: No correlation was seen between body mass index (BMI) and the incidence of PONV. BMI was negatively correlated with the time to meet ASC discharge criteria ($p = 0.02$). Increased weight and fat content have been shown to positively correlate with nausea and vomiting (Andrews, 1992; Lerman, 1992). The lack of a correlation between BMI and PONV may reflect this study's inclusion criteria which avoided the extremes of weight. It is not known why BMI was negatively correlated with the time to meet ASC discharge criteria.

4. Motion sickness: A history of motion sickness was significantly correlated with vomiting in the ASC ($p < 0.05$). The correlation between a history of motion sickness and rescue medication use in the PACU approached significance ($p = 0.05$). Three of the four patients with motion sickness were in Group I ($p = 0.25$). A history of motion sickness did not significantly correlate with other variables such as time to meet discharge criteria in the PACU and ASC or Rhodes INV-2 scores. Two of the subjects with motion sickness were Asians. The results observed in this study are consistent with findings in the literature. Other investigators have also observed correlations between PONV and patient history of motion sickness (Andrew, 1992; Lerman, 1992; Rosecrans et al., 1996; Watcha & White, 1992). The correlation between motion sickness and PONV may be due to a well developed vomiting reflex arc, making these patients more susceptible to the diverse stimuli that can activate this arc (Watcha & White).

5. Race: All three Asian subjects and two of the three Hispanic subjects in this study experienced PONV. Asian race was positively correlated with emesis in the PACU ($p = 0.01$) and in the ASC ($p = 0.001$) and with the overall incidence of rescue therapy ($p = 0.03$). Because 66% of the Asian subjects in this study had a history of motion sickness, it is not known if the correlation observed may be due to their race or their history of motion sickness. It is not known whether Asian ethnicity may be a risk factor for PONV or motion sickness. No studies were found concerning the possible differences in the incidence of PONV based on ethnicity. Pharmacogenetically, it is recognized that race and heredity play an important role in patients' responses to medications. Drug pharmacokinetics and pharmacodynamics are in many cases influenced by ethnicity (Bosch, 1996; Lin, Poland, Wan, Smith, & Lesser, 1996; Smith & Mendoza, 1996). Known differences exist in the liver cytochrome p450 enzymes (which play an important role in the metabolism of many anesthetic medications) across different ethnic groups (Lin et al.; Smith & Mendoza). As an example of this, considerable cross-ethnic variability exists regarding the therapeutic and side-effect profiles of many psychotropic drugs used in clinical settings (Lin et al., 1996). Succinylcholine related prolonged apnea is one classic example where ethnicity has played an important role regarding patient responses to anesthetic medications (Lin et al.). No studies were found regarding ethnicity and its influence on PONV.

Hispanic race was positively correlated with the incidence of PACU rescue therapy ($p = 0.02$). No studies were found regarding Hispanic race and susceptibility to anesthetic drugs or PONV. None of the Hispanics in this study had a history of motion

sickness. It is not known if genetic differences may explain the higher incidence of PACU rescue therapy use observed with the Hispanic subjects.

Surgical related factors

1. Surgical site: Intraabdominal surgery, including laparoscopy, is associated with a strong incidence of PONV. The overall incidence of 69% PONV seen in this study is similar to the incidence of PONV associated with female laparoscopic surgery reported in the literature (Ding et al., 1993; Gratz et al., 1996; King et al., 1988; Lerman, 1992).

2. Surgical duration: Surgical and anesthetic times were positively correlated with increased PONV and antiemetic use. This finding is consistent with findings in the literature. A greater incidence of PONV may be due to longer exposure to anesthetic agents, prolonged fasting, or the increased pain associated with longer surgery (Lerman, 1992). The average surgical time was similar for both groups.

Anesthesia related factors

1. General anesthesia: The standardized anesthetic was made as simple as possible. The number of anesthetic agents and medications administered to the subject during surgery were minimized to avoid possible confounding variables. Andrews (1992) states that general anesthesia itself, irrespective of what agents are used, may contribute to the occurrence of PONV. The use of nitrous oxide is believed to increase the incidence of PONV (Andrews, 1992; Lerman, 1992), and was avoided in this study. Both groups received similar amounts of anesthetic agents intraoperatively.

2. Intraoperative opioid use: Opioids occupy the mu receptor sites in the CTZ resulting in stimulation of the vomiting center. Opioid use may also sensitize the CTZ to other emetogenic stimuli (Anderson & Krohg, 1976). A standardized dose of fentanyl was used in this study. Subjects received on average 2.1 mcg/kg/hour of fentanyl during surgery. The amount of fentanyl administered intraoperatively was seen to negatively correlate with the incidence of emesis after discharge from the ASC ($p = 0.02$). This result may be due to fentanyl's analgesic properties. Patients experiencing pain have greater circulating levels of catecholamines which stimulate the CTZ and result in PONV. Administration of opioid analgesics has been reported to relieve nausea (Andersen & Krohg, 1976). Consistent with this study's findings, Claxton et al. (1997) observed fentanyl to be associated with a lesser incidence of postdischarge PONV than morphine.

Postoperative factors:

1. Pain and pain medication: Both groups received similar types and amounts of pain medication with similar frequency. No correlations were observed between the use of meperidine and ketorolac and the incidence of PONV. However, morphine was positively correlated with total incidences of emesis ($p = 0.03$), incidents of emesis after discharge from the ASC ($p = 0.01$), and time to meet PACU discharge criteria ($p = 0.05$). This is congruent with the findings of Claxton et al. (1997) that morphine is associated with a greater incidence of PONV than fentanyl. Pain and administration of pain medication are both associated with PONV, therefore a balance between the two is most desirable.

This study did not have a protocol for the use of postoperative pain medications. As mentioned in Chapter I, postoperative pain management was performed by the anesthesiologist in charge of the PACU and by the patient's surgeon once the patient was admitted to the ASC. Additionally, this study did not attempt to monitor patients' pain levels. As mentioned above, no significant differences were found between both groups regarding the type, amount, or frequency of pain medication use.

2. Intravascular fluid volume: A second postoperative factor associated with PONV is decreased intravascular volume and hypotension. The investigators of this study administered a 300-500 cc intravenous fluid bolus prior to induction of anesthesia to reduce the impact of these variables.

Postoperative urinary retention

Stallard and Prescott (1988) reported an increased incidence of urinary retention in patients who had anesthetics which lasted longer than 60 minutes, as well as those who had been mechanically ventilated, received opiate analgesia, or received neostigmine-atropine for the reversal of neuromuscular block.

Postoperative urinary retention is recognized as a possible side-effect of anticholinergic drugs such as glycopyrrolate and atropine (Orko & Rosenberg, 1984). Orko and Rosenberg did not find a significant difference in micturition difficulties between atropine and glycopyrrolate groups when used as a preoperative intravenous medication and with neostigmine for reversal of neuromuscular blockade. The same premedication anticholinergic was used as the adjunct for neuromuscular block

reversal. In common reversal dosages (0.4-0.8 mg IV), atropine has not been observed to change urinary bladder pressure, spontaneous contraction or micturition threshold (Finkbeiner, Bissada, & Welch, 1977). However, in larger dosages, micturition is impaired and urinary bladder pressure cannot be maintained during voiding, resulting in a residual urine volume increase of about 1 cc/kg (Finkbeiner et al.).

This study did not monitor postoperative urinary function. Differences between the two groups regarding ability to void is not known. It is not known whether this may have been the cause for the greater time needed to meet ASC discharge criteria seen with Group I.

Strengths of the Study

The study design was sound due to its prospective, randomized, double-blind, and quasi-experimental nature. The prospective design of this study helped to control extraneous variables and allowed the investigators to inservice those involved with data collection. Because this study was randomized, the sample was more likely to represent the population under investigation.

This study was performed at a major military medical center. Due to the nature of the military's inherent multi-ethnical structure, this increased the likelihood of generalizability to the larger populations. One of the investigators was able to preoperatively screen potential candidates to ensure observance of study inclusion and exclusion criteria. Drug selection was randomized, reducing systemic and selection bias.

Investigators as well as PACU/ASC nurses were blinded to reversal agent contents minimizing potential preconception bias. The quasi-experimental structure enhanced the internal validity of the results. The patient demographics were very similar. With the exception of the reversal agent combination studied, the anesthetic technique was standardized.

The study incorporated the use of the Rhodes INV-2 self-report form to evaluate PONV after discharge, which has established construct validity and reliability. The investigators were able to contact each subject the day after surgery to obtain RINV-2 data. The patient was given a copy of the RINV-2 form and selected the appropriate description for their circumstance. This tool allowed patients to select their own responses regarding their perceived experience of PONV. The use of this tool, thus, minimized investigator-selection bias that might have otherwise been a threat to internal validity.

Involvement of the pharmacy in the preparation and randomization of reversal agents ensured that the investigators were blinded to the contents of the syringe. Each reversal combination syringe had isotonic normal saline added so that each syringe contained 15 cc of clear solution. Thus, each syringe, no matter which reversal agent was used, looked similar to prevent investigators being able to "guess" the contents. The PACU/ASC staff were inserviced in detail prior to initiation of the study regarding data collection and definition of a nausea or vomiting event enhancing inter-rater reliability.

Body mass index (BMI) was used in this study to compare the subjects in each group. The use of body mass index may be a more reliable way to measure body fat content than the measurement of body weight alone. Many investigators compare subjects according to weight rather than BMI. BMI is calculated by dividing the patients' height in meters squared by their weight in kilograms. This measurement which reflects both height and weight may give a better indicator of a patient's fat distribution than weight alone.

Weaknesses of the Study

Similar to other reversal agent clinical studies discussed in Chapter II (Ding et al., 1994; Kao et al, 1992; King et al., 1988; Salmenpera et al., 1992; Takkunen et al., 1984), the results of this study are weakened by the small number of subjects enrolled ($n = 21$).This sample size may have been too small to show a significant difference in PONV between the 2 groups. A Type II error can not be ruled out.

Strict adherence to exclusion criteria may have barred subjects who were at increased risk for PONV, such as those with decreased gastric emptying, the obese, and those with symptomatic hiatal hernia or reflux. This may limit the generalizability of these results to the larger patient population who undergo similar laparoscopic procedures.

The administration of the standard anesthetic plan by providers other than the study investigators may have inadvertently altered the inter-operator reliability. Data collection was also collected by individuals other than the study investigators.

Although the data collection technique was standardized, variability among the collectors can not be ruled out.

The administration of morphine for postoperative pain control, as well as choice of antiemetic rescue therapy, both not controlled by this study, may have been confounding variables. Both groups, however, received similar types of pain and antiemetic medications. No significant differences were observed regarding the frequency and amount of pain medications administered in both groups.

Limitations of the Study Methods

The population studied was limited to women undergoing laparoscopic procedures, thus limiting generalizability to other surgical procedures. Time was also a limitation of this study. Data collection could have continued until enrollment of the number of subjects predicted by power analysis (120) were it not for the need to adhere to a deadline of May 30, 1997.

Conclusions

The following conclusions are drawn from the results of this study. No statistically significant difference in the incidence of PONV, rescue therapy, or RINV-2 scores was observed between the two groups. It can thus be concluded that in this population, the choice of reversal agent (neostigmine-glycopyrrolate versus edrophonium-atropine) did not affect the incidence of PONV or the use of rescue therapy. The use of edrophonium-atropine apparently provided no benefit over the use of neostigmine-glycopyrrolate regarding the incidence of PONV.

The neostigmine-glycopyrrolate group took 46 minutes longer than the edrophonium-atropine group to meet ASC discharge criteria ($p = 0.04$). No correlation existed between the incidence of PONV in the ASC and the time to meet ASC discharge criteria. The increased time to meet ASC discharge criteria was not explained by statistical analysis of variables monitored in this study. Reasons for the increased time were not apparent upon examining the ASC documentation in each patient's medical record. It is concluded that the use of neostigmine-glycopyrrolate resulted in a delay in Group I's ability to meet ASC discharge criteria in a timely manner. Anticholinergic medications such as atropine and glycopyrrolate are known to block muscarinic receptors on the bladder detrusor muscle resulting in decreased bladder tone and urinary retention. Although the specific reasons for the increased time to meet discharge criteria are not known, a delay in the inability to void is one possible reason.

A history of motion sickness was significantly correlated with emesis in the ASC and rescue medication use in the PACU. This finding is consistent with current literature.

The amount of fentanyl administered intraoperatively was seen to negatively correlate with incidents of emesis after discharge from the ASC. Morphine use was positively correlated with total incidents of emesis and incidents of emesis after discharge from the ASC. It is not surprising to see the increase in emetic response with morphine as the literature well describes. However, it was interesting to observe the relative decrease in emesis associated with the use of fentanyl intraoperatively.

Race was positively correlated with emesis in the PACU and ASC, as well as with antiemetic rescue therapy in the PACU. This was indeed an interesting finding. Although investigators have documented some of the genetic differences seen across different ethnic group regarding drug pharmacokinetics and pharmacodynamics, no studies were found which investigated the relationship between ethnicity and PONV.

Characteristics such as history of motion sickness, postoperative morphine use, and other variables were found to influence the incidence of PONV and rescue therapy use seen in this study. No significant differences existed between the two groups regarding these variables. It is thus concluded that any significant findings are attributable to the use of neostigmine-glycopyrrolate versus edrophonium-atropine and are not due to other differences between the two groups.

Implications for Clinical Practice

Rapid postoperative recovery and achievement of "street" or "home readiness" is desirable in the outpatient setting. Sung, Reiss, and Tillette (1991) estimated that two thirds of all surgical procedures are performed in the ambulatory setting. Laparoscopic procedures are growing in popularity and expanding into other intra-abdominal areas (e.g., laparoscopic appendectomies and laparoscopic hernia repairs). This population has been known to have a strong incidence of PONV.

Prophylactic antiemetic administration may be indicated in high risk groups such as patients with a history of motion sickness. However, routine administration of an antiemetic in every anesthetic plan has been questioned and discouraged due to

exposure of the patient to unnecessary cost and potential undesirable effects that may complicate expedient recovery efforts.

For a 70 kg patient treated at the institution where this study was conducted, a reversal dose of edrophonium-atropine costs $3.80 more than neostigmine-glycopyrrolate. The lack of a demonstrated significant difference in the incidence of PONV seen between the two drugs would favor the use of the less expensive drug combination neostigmine-glycopyrrolate. Alternatively, should further studies confirm that the use of neostigmine-glycopyrrolate is associated with significantly longer ASC stays as compared to edrophonium-atropine, edrophonium-atropine may be a viable pharmacoeconomic choice.

Recommendations for Further Research

Postoperative nausea and vomiting will continue to be a major issue for the patient, anesthesia care provider, and health care facility. No adult clinical studies were found comparing the incidence of PONV seen between the use of neostigmine-glycopyrrolate and edrophonium-atropine. The lack of prior studies and the small sample size obtained in this study support the need for the replication of this study.

No clinical studies were found comparing the incidence of postoperative urinary retention seen between the use of neostigmine-glycopyrrolate and edrophonium-atropine. A difference between the two reversal agent combinations may have been the reason for the 46 minute longer ASC time to meet discharge criteria seen with the neostigmine-glycopyrrolate group. If further studies demonstrate significant increases in discharge times associated with neostigmine-glycopyrrolate,

this would support the use of edrophonium-atropine despite its slightly higher cost. Thus, future studies need to investigate the incidence of postoperative urinary retention after the use of neuromuscular blocker reversal agents.

The results of this study suggest that Asian and Hispanic race may be associated with an increased risk of PONV. Further studies are needed to investigate the effects of race on PONV. Racial differences in the way patients react to and metabolize medications has been reported in literature. Asians have a decrease in certain liver enzymes as compared to Caucasians. This difference in Asians has been shown to prolong the serum concentration and effect of some psychotropic medications (Lin et al., 1996). No studies, however, were found regarding the effect of ethnicity on the incidence of PONV. Many hospitals in the United States provide services to significant numbers of Asian patients as well as other non-Caucasian patients. The investigation of the influence of ethnicity on PONV would be useful to help guide practice and allow anesthesia care providers to better assess risk for PONV. If other studies obtain similar results to this study, Asian patients may be considered at high risk for PONV and might merit pretreatment with an antiemetic.

The result of this study included a negative correlation between the intraoperative dose of fentanyl and the incidence of PONV seen. Further studies are needed to confirm these results and quantify the intraoperative dose of fentanyl associated with the least incidence of PONV. Further comparison studies of fentanyl versus morphine use and the incidence of PONV would also be useful to help determine an anesthetic technique associated with the least incidence of PONV.

As discussed in Chapters II and V, motion sickness has been observed to be significantly correlated with PONV. Studies are needed to determine effective ways to decrease the incidence of PONV seen with such patients. Study variables of interest would include intraoperative and postoperative opioid administration, travel time home after discharge, and effects of antiemetic pretreatment. Future investigators should use a measurement tool such as the Rhodes Index of Nausea and Vomiting (RINV-2) or similar instrumentation that has been shown to be valid and reliable.

Summary

PONV is associated with numerous medical complications, increased cost of care, and patient dissatisfaction. The findings of this study suggest that the choice of reversal agent used (neostigmine-glycopyrrolate versus edrophonium-atropine) did not influence the incidence of PONV observed. In this study, edrophonium-atropine offered no advantages over the use of neostigmine-glycopyrrolate regarding the incidence of PONV. For unknown reasons, patients in the neostigmine-glycopyrrolate group took a significantly longer time to meet ASC discharge criteria. This finding supports the need for further investigation of these two drug combinations.

APPENDIX A

Institutional Review Board Approval

MCHK-CI (40-38a) NOV 13 1996

MEMORANDUM FOR CPT Vincent B. Bogan, AN, Department of Nursing
(ATTN: MCHK-DN), Tripler AMC, HI

SUBJECT: Approval to Initiate More Than Minimal Risk Study

1. Your clinical investigation project entitled "TAMC 2H97: Postoperative Nausea and Vomiting: Neostigmine-Glycopyrrolate vs. Edrophonium-Atropine as Neuromuscular Reversal Agent Combinations" completed required review by the Institutional Review Board (IRB) on 22 Oct 96 and is approved to start immediately.

2. **Please note that this is NOT an approval to receive extramural resources** (ie, personnel, drugs, supplies, equipment, money, and gifts from any source outside of TAMC). If any such resources are received without DA or MEDCOM approval, the individual who receives them may be found in ethics violation and prosecuted for criminal misconduct. You must coordinate extramural resource approvals with the Department of Clinical Investigation, Bldg 40, 433-6709.

3. Your study has more than minimal risk, and the medical monitor assigned is LTC Don J. Daniels, MC. (S)He has the authority to require changes to your study or even suspension of your research to protect the safety of the volunteers. It is your responsibility to keep the medical monitor continuously informed of the status of your work and in particular to immediately report any sign or symptom suggesting adverse effect or increased risk of a volunteer, whether or not that increased risk is thought to be due to the research. The medical monitor's recommendations and requests are to be complied without failure or delay; if you cannot comply, suspend all research on this protocol immediately and notify me directly. Once a safety measure is instituted, it may not be dropped without review of the Human Use Committee and command decision.

4. Should any of the volunteers experience signs or symptoms of adverse effects or illness, you must insure immediate medical referral to the appropriate Tripler AMC health care team. You must document all such occurrences, whether or not caused by your research, and report them to the Human Use Committee. Your medical monitor will advise you whether or not that report can wait for your annual review.

5. You must report your study findings, including number of patients and adverse effects, to the Human Use Committee prior to one year from this date (or earlier if required to do so by the medical monitor). You must also report your study in the TAMC Annual Report of Clinical Investigation Activities. You will be given full instructions, including schedule of reports, from the C, Clinical Investigation, 30 days prior to any report suspense.

MCHK-CI
SUBJECT: Approval to Initiate More Than Minimal Risk Study

6. Your study and its documentation, including list of volunteers and copies of the volunteers' informed consent statements, are subject to inspection at any time by your chain of command and by such inspectors of official audit agencies as obtain prior consent from this command. You must maintain your records such as to facilitate such inspections.

7. Any public presentations or publications of your work must receive prior clearance of this command. This includes academic lectures given outside TAMC, abstracts submitted to professional meetings, letters to the editor and press releases.

8. Your research study has been determined to be of potential importance to the academic and professional program of Tripler AMC. You are to give all possible priority to its completion. Should any problem arise that jeopardizes the success of your research, notify the Chief, Clinical Investigation, at 433-6709.

H Hassell
L. HARRISON HASSELL
COL, MC
Chief, Department of Clinical Investigation

APPENDIX B

In-Hospital Data Collection Form

NEUROMUSCULAR BLOCKER REVERSAL AGENT STUDY

SUBJECT #_______ SYRINGE #________ ASA........._______ DATE _______

Age...._____ Sex.........._____ Ethnicity......___________ Weight (Kg). _____ Height _____

Surgical Procedure (LTL = 1; Lap Chole = 2)...._______

Prior History of Motion Sickness? ......_____ Last Menstrual Period (where applicable)....._____

Time of Reversal Agent Administration ...._____ Education level (years) ...__________

Surgical Procedure Time: Surgery Start Time ____ Surgery End Time _____ Total Surgical Time _____

Transfer from OR to PACU:

1. How many times (if any) did patient vomit or retch? ...._____ Time of Occurrence(s) _____
2. How many times (if any) did patient complain of nausea? _____ Time of Occurrence(s) _____

PACU: **Admit Time ..... _____ Time Met d/c Criteria _____**

1. How many times (if any) did patient vomit or retch?.........._____ Time of Occurrence(s) _____

2. How many times (if any) did patient complain of nausea? _____ Time of Occurrence(s) _____

Antiemetic and Analgesic Drugs given in PACU and dose:

Time	Drug	Dose
1.		
2.		
3.		
4.		

ASC (or Ward): Admit *Time ..... _____ Time Met d/c Criteria (for ASC) _____*

1. How many times (if any) did patient vomit?.................... _____ Time of Occurrence(s) _____

2. How many times (if any) did patient complain of nausea? _____ Time of Occurrence(s) _____

Antiemetic and Analgesic Drugs Given in ASC (or ward) and Dose:

Time	*Drug*	*Dose*
1.		
2.		
3.		
4.		

APPENDIX C

Rhodes INV Form 2

RHODES INV-FORM 2

Directions: Draw a circle around or mark through the sentence in each row that most clearly corresponds to your experience. Please make *one* mark on each *line*.

I.D. Number ____________ Date ____________

Time ____________ Time of C.T. ____________

I threw up seven or more times during the last 12 hours.	I threw up five-six times during the last 12 hours.	I threw up three-four times during the last 12 hours.	I threw up one-two times during the last 12 hours.	I did not throw up during the last 12 hours.
During the last 12 hours, I have not felt any distress from retching or dry heaves.	During the last 12 hours, I have felt mild distress from retching or dry heaves.	During the last 12 hours I have felt moderate distress from retching or dry heaves.	During the last 12 hours, I have felt great distress from retching or dry heaves.	During the last 12 hours I have felt as severe distress from retching or dry heaves as can be.
During the last 12 hours I have felt as severe distress from vomiting as can be.	During the last 12 hours I have felt great distress from vomiting.	During the last 12 hours I have felt moderate distress from vomiting.	During the last 12 hours I have felt mild distress from vomiting	During the last 12 hours I have not felt any distress from vomiting.
I have not felt nauseated or sick at my stomach during the last 12 hours.	I have felt nauseated or sick at my stomach for one hour or less during the last 12 hours.	I have felt nauseated or sick at my stomach for two-three of the last 12 hours.	I have felt nauseated or sick at my stomach four to six of the last 12 hours.	I have felt nauseated or sick at my stomach more than six of the last 12 hours.
During the last 12 hours I have not felt any distress from nausea/sickness at my stomach.	During the last 12 hours I have felt mild distress from nausea or sickness at my stomach.	During the last 12 hours I have felt moderate distress from nausea or sickness at my stomach.	During the last 12 hours I have felt great distress from nausea or sickness at my stomach.	During the last 12 hours I have felt as severe distress from nausea or sickness at my stomach as can be.
During the last 12 hours, I produced a *very large* (3 cups or more) amount each time I threw up.	During the last 12 hours, I produced a *large* (2-3 cups) amount each time I threw up.	During the last 12 hours, I produced a moderate (½-2 cups) amount each time I threw up.	During the last 12 hours, I produced a *small* (up to ½ cup) amount each time I threw up.	During the last 12 hours, I did not throw up.
I have felt nauseated or sick at my stomach seven or more different times during the last 12 hours.	I have felt nauseated or sick at my stomach five-six different times during the last 12 hours.	I have felt nauseated or sick at my stomach three-four different times during the last 12 hours.	I have felt nauseated or sick at my stomach one-two different times during the last 12 hours.	I have not felt nauseated or sick at my stomach during the last 12 hours.
During the last 12 hours I have had NO periods of retching or dry heaves without bringing anything up.	During the last 12 hours I have had 1-2 periods of retching or dry heaves without bringing anything up.	During the last 12 hours I have had 3-4 periods of retching or dry heaves without bringing anything up.	During the last 12 hours I have had 5-6 periods of retching or dry heaves without bringing anything up.	During the last 12 hours I have had 7 or more periods of retching or dry heaves without bringing anything up.

Verna A. Rhodes, RN, EdS

THE RHODES INDEX OF NAUSEA AND VOMITING

The Rhodes Index of Nausea and Vomiting Form 2 (INV) is an 8-item, 5-point Likert-type self-report pencil and paper tool that measures the patient's perceived (a) duration of nausea, (b) frequency of nausea, (c) distress from nausea, (d) frequency of vomiting, (e) amount of vomiting, (f) distress from vomiting, (g) frequency of dry heaves, and (h) distress from dry heaves. Total scores for nausea, total scores for vomiting, total scores for dry heaves, and subscale scores for each can be derived from the INV.

Subjects should be instructed to mark through or draw a circle around the sentence in each row that most clearly corresponds to their experience or describes how they feel. The tool is designed to be administered every 12 hours. The subject should be asked to choose the best hour for his/her schedule. Beginning with the chosen hour, the subject should complete one INV Scale every 12 hours at the same clock hour for the desired length of time.

The INV Form is designed to be folded in thirds to display instructions on the back of the form. The form can be conveniently placed in a pocket or purse.

In order to score the INV, reverse items 1, 3, 6, and 7. Then assign a numeric value to each response from 0, the least amount of distress, to 4, the most distress. Total distress from nausea and vomiting is calculated by summing the patient's responses to each of the 8 items on the INV. The potential range of scores is from a low of 0 to a maximum score of 32. A total symptom experience score is derived from the total score on the INV. Subscale scores also can be obtained from the INV for the following:

Subscales for Symptom Experience	Items on Scale	Potential Range of Scores
Nausea experience	4, 5, 7	0-12 4
Vomiting experience	1, 3, 6	0-12
Retching experience	2, 8	0-8
Total Experience Score	All Items	0-32

Subscales for Symptom Occurrence	Items on Scale	Potential Range of Scores
Nausea experience	4, 7	0-8
Vomiting experience	1, 6	0-8
Retching experience	8	0-4
Total Occurrence Score	All Items	0-20

Subscales for Symptom Distress	Items on Scale	Potential Range of Scores
Nausea experience	5	0-4
Vomiting experience	3	0-4
Retching experience	2	0-4
Total Distress Score	All Items	0-12

APPENDIX D

Permission to Use the Rhodes INV

Charles and Josie Smith Sinclair School of Nursing
UNIVERSITY OF MISSOURI-COLUMBIA

S446 School of Nursing Building
Columbia, MO 65211

Telephone: (573) 882-0226 FAX: [573] 884=4544

September 10, 1996

Vincent Bogan, Captain, Army Nurse Corps
Nursing Education and Staff Development
U.S. Army/University of Texas-Houston Health Science Center
Program in Anesthesia Nursing
1 Jarrett White Road
Tripler Army Medical Center
TAMC, HI 96589-5000

Dear Captain Bogan:

In response to your Fax and telephone message I am enclosing a copy of the Rhodes Index of Nausea and Vomiting Form 2 (INV), an order form, and instruction for administering and scoring the INV. While there are no costs for the use of the instrument, a copy of your data is expected in order to improve the psychometrics of the tool. As you know, the tool cannot be copied--thus the order form. Proper citation of the instrument's authorship, reliability and validity is expected. It has been a pleasure to support other Tripler Army Medical Center nursing anesthesia research projects, although at this point in time I have not received any data to determine the effectiveness of the tool within the previous studies. You will be interested to know that we are currently collecting data to develop reliability and validity on a new format for the Rhodes Index of Nausea, Vomiting, and Retching (RINVR). We would expect this tool to have high validity and reliability since it is largely a matter of making the tool easier to read. In the event that you have additional questions or concerns, you may contact me by phoning or Faxing the above numbers.

Sincerely,

Verna A. Rhodes/ld

Verna A. Rhodes, RN, EdS, FAAN
Associate Professor

VAR:ld

Enclosures

APPENDIX E

Informed Consent Form

VOLUNTEER AGREEMENT AFFIDAVIT

For use of this form, see AR 70-25; the proponent agency is OTSG

PRIVACY ACT OF 1974

Authority: 10 USC 3013, 44 USC 1101, and 10 USC 1071-1087.

Principle Purpose: To document voluntary participation in the Clinical Investigation and Research Program. SSN and home address will be used for identification and locating purposes.
preclude your voluntary participation in the investigational study.

Routine Uses: The SSN and home address will be used for identification and locating purposes. Information derived from the study will be used to document the study, implementation of medical programs, adjudication of claims and for the mandatory reporting of medical conditions as required by law. Information may be furnished to Federal, State and local agencies.

Disclosure: The furnishing of your SSN and home address is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide the information may

PART A(1) - VOLUNTEER AFFIDAVIT

Volunteer Subjects in Approved Department of the Army Research Studies

Volunteers under the provisions of AR 40-38 and AR 70-25 are authorized all necessary medical care for injury or disease which is the proximate result of their participation in such studies.

I, ______________________, SSN ____________,
having full capacity to consent and having attained my ______ birthday, do hereby volunteer/give consent as legal representative for ______________________ to participate in ________
An investigational study entitled "Comparison of the Effects of Neostigmine-Glycopyrrolate versus Edrophonium-Atropine on the Incidence of Postoperative Nausea and Vomiting
(Research Study)

under the direction of Vincent Bogan (CPT, Army Nurse Corps)

conducted at Tripler Army Medical Center
(Name of Institution)

The implications of my voluntary participation/consent as legal representative; duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by:

____

I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. Should any further questions arise concerning my rights/the rights of the person I represent on study-related injury, I may contact:

Center Judge Advocate (808)433-5311

at Tripler Army Medical Center, Tripler AMC, HI 96859-5000
(Name, Address and Phone Number of Hospital (Include Area Code))

I understand that I may at any time during the course of this study revoke my consent and withdraw/have the person I represent withdrawn from the study without further penalty or loss of benefits; however, the person I represent may be required (military volunteer) or requested (civilian volunteer) to undergo certain examinations if, in the opinion of the attending physician, such examinations are necessary for my/the person I represents health and well-being. My/the person I represents refusal to participate will involve no penalty or loss of benefits to which I am/the person I represent is otherwise entitled.

PART A(2) - ASSENT VOLUNTEER AFFIDAVIT (MINOR CHILD)

I, ______________________, SSN ____________,
having full capacity to consent and having attained my ______ birthday, do hereby volunteer for ______
______________ to participate in ______________________

____
(Research Study)

____

under the direction of ______________________
conducted at ______________________
(Name of Institution)

(Continue on Reverse)

PART A(2) - ASSENT VOLUNTEER AFFIDAVIT (MINOR CHILD) (cont.)

The implications of my voluntary participation; the nature, duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconvenience and hazards that may reasonably be expected have been explained to me by

I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. Should any further questions arise concerning my rights I may contact

at

(Name, Address and Phone Number of Hospital (Include Area Code)

I understand that I may at any time during the course of this study revoke my assent and withdraw from the study without further penalty or loss of benefits; however, I may be requested to undergo certain examination if, in the opinion of the attending physician, such examinations are necessary for my health and well-being. My refusal to participate will involve no penalty or loss of benefits to which I am otherwise entitled.

PART B - TO BE COMPLETED BY INVESTIGATOR

INSTRUCTIONS FOR ELEMENTS OF INFORMED CONSENT: (Provide a detailed explanation in accordance with Appendix E, AR 40-38 or AR 70-25).

Participant Information: You have been invited to participate in a clinical investigational/research study conducted at Tripler Army Medical Center. It is very important that you read and understand the following general principles that apply to all participants in our studies, whether normal or patient volunteers: (a) your participation is entirely voluntary; (b) you may withdraw from participation in this study at any time; refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled; (c) after you read the explanation, please feel free to ask any questions that will allow you to clearly understand the nature of the study.

Nature of Study: The purpose of this study is to determine whether or not there is a difference in the number of episodes of nausea and vomiting experienced after surgery between the use of two commonly used and accepted muscle relaxant reversal medications: neostigmine-glycopyrrolate versus edrophonium-atropine. Both drug combinations are routinely used to reverse muscle relaxation after surgery as a standard of care. Although both drug combinations have been used routinely in anesthesia for many years, to our knowledge, no previous studies similar to this one have been performed in adults to see which works best.

(CONTINUES ON ATTACHED PAGE)

I do do not (check one and initial) consent to the inclusion of this form in my outpatient medical treatment record

SIGNATURE OF VOLUNTEER	DATE	SIGNATURE OF LEGAL GUARDIAN
PERMANENT ADDRESS OF VOLUNTEER	TYPED NAME OF WITNESS SIGNATURE OF WITNESS	DATE

Volunteer Agreement Affidavit (cont.)

Expected duration of your participation: For the purposes of this study, you will not need to remain in the hospital, unless your physician requires it. The day following anesthesia you will be contacted by the telephone by one of the investigators. The purpose of the contact will be to collect information regarding any nausea or vomiting you may have experienced. Your participation in the study will end at that time. If you do not have a phone, we request you return the information form to us in the stamped, self-addressed envelope provided.

What Will Be Done: Prior to anesthesia one of the investigators will conduct an interview/physical exam. A detailed explanation will be given and all your questions regarding this study will be answered. At this time, you will be asked to sign a consent form, stating you agree to take part in this investigation.

As a study participant, you will be randomly (by chance) assigned to one of two groups. Group 1 will receive Neostigmine-Glycopyrrolate for reversal of muscle relaxation. And Group 2 will receive Edrophonium-Atropine for reversal of muscle relaxation. Both of these drugs are normally used in the reversal of muscle relaxation at the end of surgery. A muscle relaxant drug allows the skeletal muscles to become slack which allows the surgeon to easily work around them during surgery. Medications are needed to reverse the effects of muscle relaxation at the end of the surgery. These medications will be given by I.V. prior to your awakening from anesthesia to help regain your muscle strength prior to removal of the supportive breathing tube and transport to the Recovery Room. Other medications will be given during your anesthesia and will be exactly the same for all participants. Both groups will receive exactly the same monitoring during and after anesthesia. Even if you are not in this study, due to the type of surgery you are having, you will still be given muscle relaxants at the beginning of surgery and as well as drugs to reverse the muscle relaxation at the end of surgery. As mentioned above, these are needed to allow safe conduct of surgery followed by normal muscle function for breathing after surgery. If this explanation is not clear to you, please ask your anesthesia care provider for further clarification.

Neither your nurse anesthetist or the nursing staff will know what medications you have been given until the study is complete. However, for any reason necessary, we can determine which drug you received immediately by calling inpatient pharmacy.

In the recovery room you will be monitored for your recovery from anesthesia and surgery. Additionally, you will be monitored for any signs of nausea and vomiting. The recovery room nurses will ask you if you feel sick. If you do get nauseated, there are medications available in the recovery room which may make you feel better. When you are released from the recovery room , the nurses will take you to the ambulatory surgery clinic where you will also be monitored for the nausea and vomiting.

Sometimes people do not feel sick until after they leave the hospital. The day after anesthesia, your anesthetists will call you. There is a brief questionnaire, included in your packet, that will be sent home with you. The anesthetist will call and ask you to read your responses on the questionnaire over the phone. If you do not have a phone, we request you return the information form to us in the stamped, self-addressed envelope provided.

REASONABLY FORESEEABLE RISKS: There is already the risk of death with any general anesthetic. There are risks associated with general surgery and anesthesia medications, you should have

Volunteer Agreement Affidavit (cont.)

or will be informed of these risks that will be covered under a separate consent form. Risks associated with muscle relaxant reversal medications include a short period (about 30 seconds) of fast or slow heart beat, possible allergic reaction (as with any medication), or insufficient reversal of muscle relaxation.

COMPENSATION FOR INJURY: In the event of physical injury or illness resulting from the research procedure, medical treatment is available and compensation may be available. For information regarding legal aspects of participation, contact the Center Judge Advocate, at (808) 433-5311.

BENEFITS TO YOU OR OTHERS: There is no direct health benefit to you by participating in this study. The findings from the study may help other patients by finding ways to prevent or reduce the amount of nausea and vomiting. Result of this study will also contribute to the existing body of knowledge in the prevention and treatment of nausea and vomiting.

ALTERNATIVE PROCEDURES OR COURSES OF TREATMENT: If you choose not to participate in this study and still want to have your laparoscopic procedure, you will receive the anesthetic appropriate for that kind of surgery under the expected standards of care as outlined by the American Society of Anesthesiologists. If you do not wish to undergo general anesthesia, you must discuss this with your physician.

ASSURANCE OF CONFIDENTIALITY: Information gained from this study may be used as part of a scientific publication in medical or professional journals, but you will in no way be personally identified. Complete confidentiality cannot be promised, particularly to subjects who are military personnel, because information bearing your health may be required to be reported to appropriate medical or command authorities.

PRECAUTIONS TO BE OBSERVED BY SUBJECT BEFORE AND FOLLOWING THE STUDY: Your anesthesia care and medications will be standard of care for your surgery. No additional risks or precautions apply to your participation in this study.

CIRCUMSTANCES UNDER WHICH YOUR PARTICIPATION MAY BE TERMINATED WITHOUT YOUR CONSENT: (a) Health conditions or other conditions that might occur which may be dangerous or detrimental to you or your health; (b) if military contingency requires it; (c) if you become ineligible for military care as authorized by Army regulation; (d) if the safety monitor determines that continued treatment under this study may be harmful to you.

ADDITIONAL COSTS TO SUBJECT THAT MAY RESULT FROM PARTICIPATION IN STUDY: In accordance with AR 40-38, paragraph 3-3(j) (2), daily charges for inpatient care will be waived while the volunteer is in the hospital if the volunteer would not normally enter hospital for

Volunteer Agreement Affidavit (cont.)

treatment but is requested to do so as part of the research study. This also applies to the volunteer's extension of time in a hospital for a research study when the volunteer is already in the hospital.

SIGNIFICANT NEW FINDINGS: Any significant new findings developed during the course of this study which would affect your willingness to continue participation will be made available to you if you so desire. Complete results may not be known for several years.

APPROXIMATE NUMBER OF SUBJECTS INVOLVED IN THE STUDY: The goal is to include 120 subjects in this study.

DOMICILIARY CARE STATEMENT: The extent of medical care provided, should it become necessary, is limited and will be within the scope authorized for Department of Defense (DOD) health care beneficiaries. Necessary medical care does not include domiciliary (home or nursing home) care.

FOR FURTHER INFORMATION: Please contact the principal investigator or the faculty advisor:

CPT Vincent Bogan	CPT Wendell Holladay
Principal Investigator	Faculty Advisor
433-2132	433-2132

IF THERE IS ANY PORTION OF THIS EXPLANATION THAT YOU DO NOT UNDERSTAND, ASK THE INVESTIGATOR BEFORE SIGNING. A COPY OF THE VOLUNTEER AGREEMENT AFFIDAVIT WILL BE PROVIDED TO YOU.

I have read the above explanation and agree to participate in the investigational study described.

Typed Name & Signature of Volunteer ____________ Date ____________

Typed Name & Signature of Witness ____________ Date ____________

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Vita

Vincent Bernard Bogan was born in Buffalo, New York on July 8, 1960, the son of Mary Bogan and William John Bogan. After completing a general equivalency diploma in 1979, he entered the United States Army. During the period of 1980 through 1983, he performed duties as a field medic and squad leader. He worked as an Army flight medic from 1983 to 1990. He completed paramedic training in 1984 and earned a bachelors of arts with a major in Business Management in May 1990 from University of Maryland (Asian Division). He then attended Stephen F. Austin University in Nacogdoches, Texas earning a bachelors of science degree majoring in Nursing in May, 1992. He spent the following three years stationed at Bayne-Jones Army Community Hospital working as an ICU staff nurse. During this time period he worked various part-time jobs as well in areas including emergency room, medical/surgical nursing, surgical intensive care, and geriatric psychiatric nursing. In September, 1995, he entered the Master of Nursing program at the University of Texas Health Science Center at Houston in conjunction with the Army Graduate Program in Anesthesia Nursing. In 1987, he married Chae W. Ahn of South Korea. A daughter, Christine Maria Bogan was born in 1987. A son, Brian Bogan was born in 1989.

Vita

Michael W. Luce was born in Salt Lake City, Utah on December 2, 1961, the son of John LaMar Luce and Belva Rae (Williams) Luce. He graduated from Granger High School, West Valley City, Utah in 1979. He enlisted in the Utah National Guard in 1982 and was trained as an operating room technician and later as an LPN. He was employed at L.D.S. Hospital in Salt Lake City until completion of his Associate Degree in Nursing from the University of the State of New York in January of 1988. After returning from Operation Desert Shield/Storm, he was commissioned as 2nd lieutenant in the Utah National Guard. During the following years, he mainly worked for the University of Utah Medical Center, Salt Lake City, Utah, in the operation room and intensive care units, with various traveling nurse assignments in California and Nevada. He received his Bachelor of Nursing degree from the University of Phoenix, Utah Campus in May, 1994. He continued to work at the University of Utah Medical Center until he entered the U.S. Army/University of Texas at Houston Anesthesia Nursing Program where he is currently enrolled. In 1983, he married Sydney J. Pedersen of Salt Lake City, Utah. They have one daughter Melinda, born in 1981, adopted by Michael, and two sons: Bryan J., born in 1984, and Jonathan C., born in 1986.